EXHIBIT A

EXPERT REPORT OF MARIANNE MANN, M.D.

I have been asked to review materials related to the approval, post marketing surveillance, and labeling revisions for certain products containing olmesartan medoxomil manufactured, marketed and sold by Daiichi Sankyo (DSI). My understanding is that the Court has asked the parties to only address issues of causation at this time and my report will focus on those issues from an FDA regulatory perspective. I reserve the right to supplement this report based on the receipt of new information or as otherwise needed. I am being compensated to serve as an expert witness in this matter at an hourly rate of $600.00

MY QUALIFICATIONS

As per the attached CV (Appendix A), I am a physician, board-certified in internal medicine. I obtained my MD in 1986 after completing an accelerated six-year BA-MD program at Lehigh University and the Medical College of Pennsylvania. I then trained as a medical resident and fellow for six additional years through 1992. My residency was in internal medicine, and was completed at Albert Einstein Medical Center (Philadelphia), and the University of Connecticut Health Center. My fellowship was in Pulmonary and Critical Care Medicine, completed in 1992 at the University of Connecticut Health Center. From 1992 to 1994, I worked as a clinician largely in the critical care (ICU) setting.

In 1994, after approximately eight years of clinical training and practice as a physician, I joined the FDA. I worked at the FDA for nine years through 2003. I began in the Division of Antiviral Drug Products from 1994 to 1997 as a primary medical reviewer. In this role, I reviewed clinical data carefully and thoroughly in order to come to conclusions about drug efficacy and safety. I reviewed Investigational New Drug Applications (INDs), New Drug Applications (NDAs) and supplemental NDAs (sNDAs) during those three years, including assessing clinical development programs, protocol designs, and trial results. I was the primary reviewer for dozens of IND submissions and approximately five NDAs. I presented at Advisory panel meetings on behalf of the Agency. I was fortunate to be selected to participate in a new medical officer leadership program at the Center for Drug Evaluation and Research (one of approximately 20 participants). As a medical officer, I was primarily responsible for following post-marketing drug safety reports related to my drugs and deciding if a safety signal was becoming noteworthy. While at the Agency, I received several awards, including a high-level FDA award in 1998, the Department of Health and Human Services Secretary's Award (given by Donna Shalala, Secretary of the Department of Health and Human Services).

In 1997, I was promoted to Deputy Director of the Division of Reproductive and Urologic Drug Products (DRUDP). I remained in this position through 2000. This position is essentially "second in command" of a review division, serving under the director and sometimes in place of the director. As a Deputy Director, I participated in final decisions such as whether to place a study on hold or whether to approve/not approve a drug, and whether to update/change labeling for a drug. I presented at additional Advisory panel meetings and was selected to teach a course on this for clinicians at the FDA. I helped address drug safety concerns, including those that arose in the post-marketing setting. I had experience in dealing with drug safety issues as both a primary reviewer (having several products under my responsibility) and as a Deputy Director. I chaired the FDA's internal safety working group for Viagra for its post-marketing safety concerns. Safety issues were managed with labeling updates and other risk management considerations, and involved a comprehensive multidisciplinary FDA team approach including working with the sponsor.

In 2000, I became the Deputy Director (same role) in the Division of Pulmonary and Allergy Drug Products where I remained until 2003. While in this role, I was also Acting Director for approximately two months. Similar to my role in DRUDP, I was an integral member of teams that would address many issues, including handling post-marketing safety concerns. In total, I had nine years of FDA experience in three different review divisions. I was centrally involved in or the primary decision maker for key regulatory challenges such as IND holds, NDA approval/non-approvals, labeling (which was a key focus of the job), and major protocol design issues. Among many other issues, I managed premarketing and post-marketing drug safety concerns either as the head of a team or part of a team within the FDA.

In 2003, I left the Agency to become branch chief of the respiratory disease branch at the National Institutes of Health (NIH). As branch chief, I was in charge of creating a cohesive and directed research program for a set of respiratory diseases, including SARS and avian influenza. While at NIH, I was involved in drug development and filed several INDs (as a sponsor) to FDA to pursue NIH-funded research. This experience included working with FDA, enrolling subjects into clinical trials, meeting with investigators, and managing the many additional issues that arise when performing clinical investigations.

In 2004, after more than a decade of work for the federal government, I became an independent consultant. Since 2004, I have worked with numerous pharmaceutical companies to facilitate the safe and effective development of drugs. Some of my work with industry has focused on post-market safety issues. In these cases, I have worked as a consultant with sponsors to prepare them to work with the FDA and address the safety concern with reasonable labeling and/or risk management plans.
Within the past decade as a consultant, I have also worked as a testifying expert. In the past four years, I have given a deposition in Washington D.C. in the Reglan litigation on February 13, 2013 (Gardley-Starks v. Pfizer, U.S. District Court, Northern District of Mississippi). I gave a second deposition in the Reglan litigation in Washington D.C. on July 29, 2016 (King v. Pfizer, Inc. et al., U.S. District Court, District of Nebraska which was cross-noticed in Sherman v. Pfizer, Inc. et al., Superior Court of Washington, Grays Harbor County). I have never given trial testimony.

MATERIALS REVIEWED

- See Appendix B, attached hereto.

OVERVIEW OF FDA SAFETY REGULATION AND REVIEW PRACTICES

It is the mission of the FDA to protect the US public health by assuring the safety, efficacy, and security of human and veterinary drugs, vaccines and other biological products, medical devices, the food supply, cosmetics, and products that emit radiation. FDA is also responsible for advancing the public health by helping to speed innovations that make medical products more effective, safer, and more affordable and by helping the public get the accurate, science-based information they need to use medical products and foods to maintain and improve their health.[1] To meet these responsibilities, FDA has a staff of over 16,000 personnel and an annual operating budget of nearly $5 billion.[2]

[1] http://www.fda.gov/aboutfda/whatwedo/

[2] http://www.hhs.gov/about/budget/budget-in-brief/fda/index.html#.

The Center for Drug Evaluation and Research (CDER) is the largest organization within the FDA and encompasses approximately 3600 employees in various Offices and Divisions.[3] Its job is to determine for each drug that its benefits outweigh its risk and to approve the drug with appropriate labeling.[4] Based on authority derived from the Federal Food, Drug, and Cosmetic Act, the FDA promulgates regulations, policy statements, guidelines, guidances and other pronouncements to guide the pharmaceutical industry in implementing the specific provisions of the Act. The FDA, through CDER, has the responsibility of reviewing and approving new drugs and for post-approval oversight of marketed drugs. Safety of any drug is a key aspect of the FDA's review from the first study in humans throughout the approval of the product and post-approval.

Within CDER, the Office of New Drugs is responsible for the primary review and evaluation of new drug products. There are approximately fifteen primary drug review divisions within CDER, each with different areas of expertise. A drug review division is the central unit responsible for assessing the safety and efficacy of drug products. A typical CDER review division includes scientists from a variety of backgrounds who interact with each other to fully understand a drug from many perspectives. These scientists include chemists, animal toxicologists, bio-pharmacists, pharmacists, statisticians, and clinicians. The CDER Division responsible for olmesartan was the Division of CardioRenal Drug Products.

Within each CDER discipline, there is a layered structure of primary reviewers and team leaders and those with higher levels of oversight. The teams come to final decisions about a product after obtaining input from each team member. Most of the final decisions about drugs are made by the Division Director who also has oversight from higher level CDER authorities. For a new chemical entity, the final approval decision is made by the Office Director. Olmesartan was a new chemical entity when it was initially approved, yet it was not the first ARB (angiotensin receptor blocker) that FDA had seen. Therefore, this particular drug class was well understood.

The process to bring a new drug to market is a complex, highly regulated and time consuming one. In brief, drug companies seeking approval to sell a drug in the United States must test it in a number of ways. First, the drug company or sponsor performs laboratory and animal tests to discover how the drug works and whether it's likely to be safe and work well in humans. Next, a series of tests in humans is begun to determine whether the drug is safe when used to treat a disease and whether it provides benefit. The company then sends the results of these tests to the FDA in a New Drug Application (NDA)[5] so that the agency can evaluate the drug.

Once a new drug application is filed, an FDA review team from the various divisions within the Office of New Drugs within CDER--medical doctors, chemists, statisticians, microbiologists, pharmacologists, epidemiologists, supervisory review officers, Division Directors, Office Directors and other experts--evaluates whether the studies the sponsor submitted show that the drug is safe and effective for its proposed use. The review process can take from six to twelve months or longer to complete.

In addition to the data and information submitted by the sponsor in the NDA, the FDA reviewers will

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[3]http://www.fda.gov/downloaDSI/AboutFDA/ReportsManualsForms/Reports/BudgetReports/UCM3015.pdf

[4] http://www.fda.gov/AboutFDA/Transparency/Basics/ucm213161.htm.

[5] 21 CFR 314.

also rely on other information that may be relevant to their review of the drug in question such as the published scientific and medical literature. Also, importantly, for a drug such as olmesartan, FDA will also call upon its historical knowledge of the development, clinical studies, safety profile, and post-marketing surveillance of drugs in the same pharmacologic class (ARBs) and other classes of antihypertensive agents. This knowledge forms a foundation to which the reviewers compare a new entry to the class such as olmesartan to ensure that the benefit/risk ratio of the new product is acceptable.

If approved, a prescription drug is accompanied by FDA-approved labeling, a compilation of information about the product, based on the FDA's thorough review of the NDA marketing application. In collaboration with the sponsor, the FDA takes great care and attention to crafting an accurate yet focused label that reflects the drug's benefits and risks. The FDA recognizes that a drug's labeling cannot contain everything that is known about a drug. Such labeling would be too voluminous to be useful.[6] It is meant to provide a summary for the healthcare practitioner of the actions of the drug in humans and relevant safety, efficacy and use information so that a health professional can appropriately weigh the benefits and risks of the drug for individual patients.[7] The label also governs what may be included in promotion and advertising materials related to the drug. The FDA has the final say on all labeling prior to a product's approval.

The sponsor is required to submit a supplemental new drug application (sNDA) if it wishes to change a label, market a new dosage or strength of a drug, or change the way it manufactures a drug. Prior to implementing these changes, the FDA reviews the sponsor's sNDA application. Sponsors can submit supplemental NDAs for such labeling changes or, alternatively, a more immediate change can be implemented to the label as a "changes being effected" (CBE) supplement. Olmesartan products underwent many labeling changes under either supplemental NDA applications or as CBE supplements. Each of these supplemental NDA approvals by the FDA entails a thorough overview of the package insert, during which time the FDA has the ability to readily make any changes it deemed necessary. The multiple approved supplements for olmesartan products supports that the FDA considered (and reconsidered, multiple times) the package insert to assure it accurately reflected the key benefit/risk information.

The FDA's evaluation of drug products does not end with marketing approval. Active investigation of the product continues throughout the life cycle of a drug, from its initial development in controlled clinical trials through to its post-marketing real-life experience. The FDA sets standards for testing, reporting and communication. Manufacturers are required by the FDA to have systems to detect, assess, and follow-up on safety issues. The FDA has particularly rigorous standards on the reporting requirements for post-marketing surveillance. The FDA inspects and audits company clinical trials and post-market surveillance systems to assure the integrity of the process.

In the post approval period, the FDA may learn more about the drug's risks as reflected by the medical literature, and from post-market safety reports, ongoing clinical trials, registries, etc. Because the FDA

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[6] Guidance for Industry – Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products – Content and Format, January 2006, pp. 2,5.

[7] 21 CFR 201.56(a).

has access to data relating to all drugs in a given class, it often has access to more data than any given sponsor. Rare risks may arise as safety signals only when more patients are exposed. This limitation is accepted for drugs at the time of their approval as long as the benefits of the drug outweigh its known risks. The Agency (as well as sponsors) continue to follow the product for safety signals closely as it is used more widely in the real-life setting, and as it is evaluated in other clinical trials and/or epidemiologic studies or active surveillance evaluations. This practice is known as pharmacovigilance.

Adverse drug events are entered into a database called the FDA Adverse Event Reporting System (FAERS).[8] While FAERS is a highly useful tool to support the FDA in its safety surveillance activities, it does have limitations.[9] The FDA does not require that a direct causal relationship between the reported event and the suspect drug be established before a report is submitted and entered into the FAERS database. Thus, there is no certainty that the reported event was actually due to the product. Reports also do not always contain enough detail to properly evaluate an event. Factors such as the time a product has been on the market, adverse events with similar products or publicity about a safety issue can all impact the reporting of adverse events to FDA.

As FDA stated in a Guidance on pharmacovigilance:

> For any individual case report, it is rarely possible to know with a high level of certainty whether the event was caused by the product. To date, there are no internationally agreed upon standards or criteria for assessing causality in individual cases, especially for events that often occur spontaneously (e.g. stroke, pulmonary embolism). Rigorous pharmacoepidemiology studies, such as case-control studies and cohort studies with appropriate follow-up, are usually employed to further examine the potential association between a product and an adverse event.[10]

Indeed, adverse event Form FDA 3500A, also known as a "MedWatch" form that pharmaceutical manufacturers must use to report adverse events, states in bold on the first page: "Submission of a report does not constitute an admission that medical personnel, user facility, importer, distributor, manufacturer, or product caused or contributed to the event."[11]

In many ways, the post-market adverse event reports are the most challenging and difficult to assess in ascertaining if a drug-related safety signal is present, as they are uncontrolled and subject to confounding medical conditions and/or medications. Furthermore, the quality of information provided by these reports is frequently incomplete and inferior to the quality of data provided by randomized clinical trials or more carefully controlled observational studies. Adverse event reports are particularly

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[8]http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm.

[9]http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm.

[10] Guidance for Industry: Good pharmacovigilance practices and pharmacoepidemiologic assessment, March 2005.

[11] Form FDA 3500A.

problematic for attempting to draw causal inferences, as they may be submitted by anyone (a patient, a provider, a layperson, an attorney), and because they are not validated in any way, and the accuracy of the reports is unknown (and is usually not verifiable). Therefore, information from reported adverse events is generally considered less valid than information derived from well controlled randomized trials and/or observational studies.

Every FDA-approved medication – both prescription and non-prescription – carries the risk that persons taking that drug may experience an adverse event while on the medication. Some key factors that are considered in assessing if a drug is causally associated with an adverse event are:

- The mechanism of action of the drug is considered. If a drug has a plausible mechanism for a particular adverse event finding, this supports attribution to the drug.
- Preclinical animal data are considered.
- Placebo-controlled clinical trials are considered.
- Open-label longer term safety trials are also considered.
- The clinical experience with the broader drug class is also considered.
- The medical literature is evaluated and considered.
- If the only evidence derives from post-marketing adverse event reports, the quality of the information in the adverse event report, and whether confounding medical diagnoses or confounding medications also may cause the adverse event are considered carefully.
- The actual adverse event itself is also considered. Certain adverse events are known to result from drugs and present with objective clear evidence from laboratory values or a very precise and objective clinical presentation. Examples include hepatotoxicity, seizures, anaphylaxis, or severe skin rashes such as Stevens Johnson Syndrome. These safety signals, if they arise in the post-market setting, may be recognized more readily as drug-related adverse events. Adverse events that are not known to be related to drugs or that present as more common subjective complaints may be more challenging to attribute immediately to a drug.
- A close temporal relation of the patient taking the drug and the onset of the adverse event supports that an event is drug-related. This is particularly the case when the event is something like nausea, vomiting, diarrhea, or weight loss. These types of GI symptoms, if drug-related, generally would arise soon after a patient begins taking a drug.
- Dechallenge (resolution of an adverse event upon stopping the drug) and rechallenge (recurrence of the adverse event upon restarting the drug) are also factors but are not the sole evidence that one relies upon. Rather, this is part of a larger picture that is considered. The event itself also needs to be considered when a report concludes that a positive dechallenge or positive rechallenge is present. Objective and less common events, such laboratory evidence of lower liver function tests upon dechallenge and raised liver function tests upon rechallenge, can be compelling evidence of a drug-related adverse event. Subjective and more common events, such as abdominal pains or diarrhea, may be more difficult to interpret in the setting of dechallenge and rechallenge, as they may be influenced by other factors.

In 2007, the FDA began sharing potential signals of new safety information from FAERS through a new information technology platform called the Document Archiving, Reporting, and Regulatory Tracking System (DARRTS), which allows CDER reviewers to share information, project plans, document reviews

and recommendations for regulatory action.[12] DARRTS allows for a collaborative review of information about potential drug safety issues across CDER review disciplines. CDER may decide to create a Trackable Safety Issue (TSI) within DARRTS to follow the evaluation of an issue throughout the Center. A TSI can be created when the issue might potentially lead to one of the following:

- Withdrawal of an approved drug from the market;
- Withdrawal of an approved indication;
- Limitations on use in a specific population or subpopulation;
- Additions or modifications to the Warnings and Precautions or Contraindications sections of the labeling, or the Medication Guide or other required Patient Package Insert, including safety labeling changes required under the Food and Drug Administrative Amendments Act (FDAAA);
- Establishment of or changes to the proprietary name/container label/labeling/packaging to reduce the likelihood of medication errors;
- Establishment or modification of a risk evaluation and mitigation strategy (REMS);
- A requirement that a sponsor conduct a safety-related post-marketing trial or study; or
- The conduct of a safety-related observational epidemiological study by FDA.[13]

The appearance of a drug on the TSI listing does not mean that the FDA has concluded that the drug has the listed risk. It simply means that the FDA has identified a potential safety issue, but it does not mean that the FDA has identified a causal relationship between the drug and the listed risk. When a TSI is opened, the sponsor is notified and the public is subsequently notified through the posting of a quarterly listing of all new TSIs on the FDA AERS website.[14] Once the CDER reviewers complete their evaluation and determine what regulatory action is warranted, if any, then that action is implemented in concert with the drug manufacturer and the TSI is closed.[15] It is not unusual that the conclusion by the FDA at the end of a TSI investigation is that no regulatory action be taken.[16]

REVIEW OF OLMESARTAN PACKAGE INSERTS AND CLINICAL DATA FROM NDA SUBMISSIONS

The FDA clinical reviews of each of the products that contain olmesartan medoxomil and the integrated safety summaries for each product were carefully assessed for safety findings. A review of approved labeling and the clinical data submitted by DSI for each product follows below, along with key GI findings from clinical reviews performed by the FDA.

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[12] Guidance – Classifying Significant Post-marketing Safety Issues, Draft Guidance, March 2012.

[13]http://www.fda.gov/downloaDSI/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/manualofpoliciesprocedures/ucm164967.pdf.

[14]http://www.fda.gov/downloaDSI/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/manualofpoliciesprocedures/ucm248882.pdf.

[15]http://www.fda.gov/downloaDSI/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/manualofpoliciesprocedures/ucm164967.pdf.

[16] *Id.*

BENICAR: Approved April 25, 2002

Benicar was developed under an IND opened May 1, 1995. Benicar was approved by the FDA on April 25, 2002. Benicar was developed in accordance with FDA guidelines, and DSI had frequent interactions with the Agency during the approval process.

Benicar is a prodrug (olmesartan medoxomil) that is metabolized to olmesartan. For this report, I will refer to the tradename Benicar or I will use the chemical name olmesartan. Both olmesartan medoxomil and olmesartan are angiotensin II receptor antagonists. Pharmacologically, Benicar had an attractive profile with once daily dosing and no observed drug: drug interactions. There were numerous parallel, placebo-controlled, fixed dose studies that showed Benicar was effective in reducing BP in patients with essential hypertension. The original approved label cited that it had been evaluated in more than 3825 patients, with about 900 treated for 6 months and over 525 treated for a year. This database exceeded FDA's recommendation at the October 27, 1998 pre-NDA meeting that Sankyo have 1500 patient exposed overall, with 600 patients exposed for 6 months and 100 patients for one year. The FDA reviewer (Dr. Stockbridge) noted in his review: "this represents a safety database similar to that of most modern era new molecular entities for the treatment of hypertension. The scope of the data obtained was also conventional."

Serious adverse events were "very rare" on Benicar in controlled studies, and the most common serious events in long term open label studies were chest pain (n=4) and angina (n=3) both of which the reviewer noted were not uncommon events in the studied population. The only adverse events leading to treatment discontinuation in more than 0.1% of patients in placebo controlled trials were dizziness (0.2%) and angina (0.2%). The most common adverse events that were more common with Benicar than placebo in controlled trials included flu like symptoms (3.1% vs 2.9%), dizziness (2.8% vs 0.9%), bronchitis (2.0% vs 1.8%), hematuria (2.0% vs 1.8%), back pain (1.6% vs 1.4%), CPK increased (1.6% vs 1.1%), and diarrhea (1.1% vs 0.7%). The highest ratios were observed for Dizziness and CPK elevation. There was no evidence in the Benicar reviews of drug related GI concerns, other than some rare patients with liver function (LFT) changes. There were no cases of celiac disease described or any signal for chronic severe diarrhea in the NDA database.

Overall, Benicar was carefully reviewed by multiple clinicians: Drs. Rodin, Targum, Williams, and Stockbridge. Dr. Temple, a higher level FDA official, also was involved in many key meetings. Benicar was also reviewed very thoroughly by multiple toxicologists, including the CAC panel who reviewed the drug multiple times. Benicar was approved on April 25, 2002. Benicar was contraindicated in patients with a history of hypersensitivity and it had a black box warning regarding its class risk during pregnancy. Warnings included class warnings about fetal/neonatal morbidity and death, hypotension in volume or salt-depleted patients, and risks of impaired renal function. Adverse reactions that occurred in more than 1% of patients (and were greater in Benicar than placebo) included dizziness (3% vs 1%). Other adverse reactions that occurred in more than 1% of Benicar patients but "at about the same or greater incidence than placebo) included: back pain, bronchitis, elevated CPK, diarrhea, headache, hematuria, hyperglycemia, hypertriglyceridemia, influenza-like symptoms, pharyngitis, rhinitis and sinusitis. Other adverse events are listed "that have been reported with an incidence of greater than 0.5%, whether or not attributed to treatment" yet observed in controlled or open label trials are listed in the label as well, and within this list are gastrointestinal events of abdominal pain, dyspepsia, gastroenteritis and nausea. Liver function changes are outlined in the label as well as small decreases in hemoglobin/hematocrit.

BENICAR/HCT: approved June 5, 2003

Benicar/HCT is a combination of olmesartan medoxomil with a diuretic, hydrochlorothiazide (HCT). For this report, I will refer to the drug as Benicar/HCT. This combination is well established as an effective combination therapy for hypertension, and each single ingredient had been approved and marketed for years in the US prior to this submission. Additionally, the FDA review noted that at least six combination products like this (angiotensin receptor blockers with a diuretic) had been approved in the US.

The NDA was reviewed separately for safety and efficacy by the FDA. The efficacy review was performed by Dr. Salma Lemtouni. The pivotal trial performed was Study CS-866-318. In her review (Page 13), Dr. Lemtouni noted "the original protocol of the pivotal study was reviewed in great detail." The combination of both ingredients was found to be superior to placebo at all dose levels evaluated.

The safety review was performed by Dr. MaryAnn Gordon. A total of 1243 patients had been exposed to the combination therapy in either phase 2 or 3 clinical trials, with a duration of exposure up to 2 years. For longer term exposure, 316 patients had been treated for at least 6 months or longer, and 112 had been treated for a year or longer. Dizziness was the only adverse event that appeared to be linked to the drug. Safety data with long term use of the product (to one year) did not change the conclusions drawn from the pivotal trial.

The FDA's findings of GI events (seen in Table 8.5.4.2.2.a) reflected the following rates of adverse events over one year of treatment with placebo versus all Benicar/HCT arms combined: diarrhea (8.8% vs 12.1% , nausea (1.5% vs 2.4%), abdominal pain (1.2% vs 2.1%), dyspepsia (1.5% vs 1.4%), vomiting (0.3% vs 1.2%), and gastroenteritis (0.8% vs 1.1%). There were no cases of celiac disease or SAEs of diarrhea noted in the FDA review.

Benicar/HCT was approved by FDA on June 5, 2003. Labeling included the black box warning for pregnancy and warnings regarding fetal toxicity. The label included a warning regarding hypotension in volume or salt-depleted patients, and a precaution regarding impaired renal function. For the HCT component, warnings regarding hepatic impairment, hypersensitivity reactions, exacerbations of lupus, and lithium interactions were described. Precautions were noted to monitor electrolytes, particularly potassium levels when on therapy, as well as risk of gout or needing to adjust diabetes medications due to changing glucose levels on therapy. Adverse drug reactions listed in a table included nausea, hyperuricemia, dizziness, and upper respiratory tract infection. Additional adverse reactions that occurred at a rate > 2% and at levels equal to or higher than placebo also included headache and urinary tract infection. Finally, adverse events that arose at rate of greater than 1% in the more than 1200 patients treated in controlled or open label trials, were also listed in the label. In this section, the GI events listed were: abdominal pain, dyspepsia, gastroenteritis, and diarrhea.

BENICAR/AMLODIPINE (AZOR): approved September 26, 2007

Azor is a dual agent combination therapy for hypertension including olmesartan medoxomil (20 or 40 mg) and amlodipine besylate (5 or 10 mg). For the purpose of this report, I will refer to the drug as Azor. Azor is indicated as initial therapy for hypertension either alone or in combination with other agents. Azor is indicated in patients likely to need multiple antihypertensive agents to achieve their blood pressure goals.

An 8-week pivotal placebo controlled factorial designed trial supported the efficacy of Azor. The study included approximately 2000 patients randomized to many treatment arms (dual or single therapy at a variety of doses) or placebo. Following the randomized 8 week study, patients were enrolled for an additional 44 weeks in an open-label continuation trial. A total of 1684 patients enrolled in this open label study, of whom 1492 were exposed for at least 6 months, and 524 were exposed for 44 weeks or longer. From a safety perspective, edema was a significant safety concern related to amlodipine, affecting 20% of patients on the combination therapy. Edema was followed by dizziness (6%), headache (4%) and hypotension (2%) for the most common adverse events.

The FDA reviewer noted that the adverse events observed with Azor were consistent with the adverse event profiles of each single ingredient, but noted three major noteworthy adverse events: edema, hypotension, and laboratory abnormalities (elevated liver function tests and platelet counts). A total of 25 patients had serious adverse events: 3 in the placebo arm, 7 in a monotherapy arm, and 15 in a combination (Azor) arm. SAE events that arose either prior to randomization or during the double-blind phase of the trial were not consistent with diarrhea or sprue. The only GI SAE event noted at all was one of GI hemorrhage in a patient treated with olmesartan 40 mg, and this event was felt unlikely to be due to study drug. As per Dr. Williams' primary medical officer review (page 55): "In the analysis of SAEs, there did not appear to be any event or trend in event that signified a safety issue within any of the treatment groups. All of the reported events were consistent with what would be expected in a hypertensive population of the age recruited for this study." Dr. Williams also noted that the adverse event profiles observed during the open label 44-week extension study were similar to those observed during the 8 week double-blind portion of the study. There were no cases of celiac disease or SAEs of diarrhea noted in the FDA review.

GI adverse events were observed during the randomized controlled study and were broken down by day 1 through week 4, and then for weeks 4-12. Overall, during day 1 through week 4, events of nausea, constipation, diarrhea and dry mouth were observed in 1-2% of patients treated with AZOR. During weeks 4-12, diarrhea, nausea, vomiting, dry mouth, constipation, dyspepsia, or gastritis were observed in 1% or fewer patients treated with AZOR.

Azor was approved by the FDA on September 26, 2007 with labeling that described specific warnings and precautions consistent with each agent that had been previously approved. Specific to GI, vomiting was noted as a post-marketing adverse event observed in association with olmesartan. Adverse reactions seen at lower rates during the double-blind period that occurred in patients treated with Azor arose at about the same or greater incidence as in patients receiving placebo. These adverse reactions included hypotension, orthostatic hypotension, rash, palpitation, urinary frequency and nocturia.

<u>BENICAR/AMLODIPINE/HCT (TRIBENZOR): approved July 23, 2010</u>

Tribenzor is a triple drug combination therapy containing olmesartan medoxomil, amlodipine besylate, and hydrochlorothiazide. It is approved at variety of strengths that were supported as safe and effective in the NDA. The triple combination was shown to be superior over the dual components in a 12 week, placebo-controlled, pivotal trial involving approximately 2500 patients. The adverse events were similar to what might be expected with the components; hypotension occurred most, however, with Tribenzor (8 reports or 1.4%) than with dual agents (3 reports or 0.5%).

There were 2304 patients evaluated for safety in the pivotal study. The mean exposure in the pivotal study was 83 days (as it was a 12-week study). Discontinuations due to adverse events were more common in the triple therapy arm (4%) than the dual-ingredient arms (1-2%). These were due to dizziness and blood pressure drops for Tribenzor. Serious adverse events arose in 1.7% of Tribenzor treated patients versus 1.2-1.6% of the dual-ingredient arms. Serious adverse events reported between weeks 4-12 included a variety of events including two GI events: duodenitis and gastritis, however most events were not in the GI category. For adverse events arising at least 3% of the time, nausea was the only GI event that was listed, affecting at most 3.8 % of patients in an olmesartan/HCTZ treatment arm. There were no cases of celiac disease or SAEs of diarrhea noted in the FDA review.

Open label trials provided long term experience with Tribenzor as well as the dual therapies. There were no cases of severe diarrhea or celiac disease reported in the FDA review of these studies. One SAE of viral gastroenteritis was observed in a patient on Tribenzor in the longer term safety dataset. In all the longer-term studies reviewed, no cases of severe diarrhea or celiac disease were described.

Labeling described the most common adverse reactions (more or equal to 2%) as including dizziness, peripheral edema, headache, fatigue, nasopharyngitis, muscle spasms, nausea, upper respiratory tract infection, diarrhea, urinary tract infection and joint swelling. Diarrhea, specifically, was observed in 2.6% of patients on Tribenzor versus 1.6% to 2.3% of patients on dual therapy. Labeling also noted that olmesartan medoxomil has been evaluated for safety in more than 3825 patients/subjects, including more than 3275 patients treated for hypertension in controlled trials. This experience included about 900 patients treated for at least 6 months and more than 525 treated for at least 1 year. Treatment with olmesartan medoxomil was well tolerated, with an incidence of adverse reactions similar to that seen with placebo. Adverse reactions were generally mild, transient, and without relationship to the dose of olmesartan.

The reviews of the four products that contain olmesartan revealed no signals in initial NDA or subsequent NDA submissions for any significant serious or severe GI disorder. Each application addressed long-term exposure to at least a year in a reasonable number of subjects and thus explored the longer term safety as well as the shorter term safety of the product. Gastrointestinal side effects were generally uncommon and balanced between treatment arms. There were slightly elevated risks for non-serious adverse GI drug reactions of diarrhea, nausea, vomiting, dyspepsia, or gastroenteritis observed with active drug vs placebo in some databases, but these events were modest in nature and were not seen consistently for every dataset. There were no findings in any olmesartan-product original NDA submissions suggestive of a safety signal for severe diarrhea, malabsorption, or celiac disease.

REVIEW OF OLMESARTAN LABELING UPDATES

As described above, DSI worked with the FDA during the course of the FDA review of the original NDA for each of the olmesartan products to develop labeling that would provide adequate directions for use to allow for the safe and effective use of the olmesartan products in the treatment of hypertension. However, drug product labeling is a dynamic entity with changes being proposed, reviewed, approved and implemented as a result of new information becoming available to the drug product sponsor and the FDA. For all four olmesartan products, numerous updates were made to the labels for safety-related findings or, less often, to extend the indication. Each time the Agency reviewed and approved these supplements, they were reviewing the entire label and approving it. The multiple labeling updates below support that both DSI and the FDA were following safety carefully.

Benicar Labeling Updates

- October 25, 2002 labeling updated the Adverse Drug Reactions section for GI symptoms in controlled or in open label trials (abdominal pain, dyspepsia, gastroenteritis and nausea) among other AEs, also updated fetal morbidity and mortality in rat pups;
- February 12, 2003 labeling updated to add information on chromosomal aberration studies and the post-marketing adverse reaction of rhabdomyolysis;
- November 12, 2004 labeling updated to add angioedema as an adverse drug reaction;
- July 13, 2005 labeling updated for the post market experience/adverse drug reaction section to add several AEs including vomiting to this section of the label;
- September 26, 2007 labeling added hyperkalemia as a post-market adverse drug reaction;
- February 4, 2010 extended the indication to pediatric patients age 6-16 years;
- May 19, 2011 added anaphylactic reactions to the post-marketing section of the label;
- June 6, 2011 added a drug reaction concern with nonsteroidal anti-inflammatory drugs;
- February 15, 2012 changed the indications and usage section to warn that children under age 1 year should not receive Benicar; additional labeling changes regarding morbidity in infants were added;
- March 29, 2012 a boxed warning on fetal toxicity was added to the label;
- September 28, 2012 a contraindication for the concomitant use of Benicar with aliskiren in diabetic patients was added to the label, and warnings about dual blockade of the renin-angiotensin system (RAA) was added;
- December 11, 2012 labeling updated a drug: drug interaction with colesevelam hydrochloride;
- July 3, 2013 “sprue like enteropathy” was added to the label;
- June 13, 2014 ROADMAP data were added to the label;
- June 27, 2014 a lithium interaction was added to the label;
- September 23, 2014 additions were made to the ROADMAP and dual RAA system areas of the label;
- November 1, 2016 hyperkalemia was added as an adverse drug reaction.

Benicar/HCT Labeling Updates

- November 12, 2004 labeling updated to include angioedema;
- July 13, 2005 labeling updated to include vomiting as a post-marketing adverse event;
- November 16, 2007 labeling updated to include hyperkalemia as a post-marketing adverse event;
- May 3, 2011 labeling updated to include Warnings about myopia and glaucoma, Precautions about nonsteroidal anti-inflammatory drug interactions and also post-marketing adverse events of anaphylactic reactions, peripheral edema, and diarrhea
- January 18, 2012 boxed warning for fetal toxicity added;
- September 18, 2012 dual blockade RAA warning added as well as aliskiren contraindication in diabetics;
- December 11, 2012 label updated for colesevelam interaction;
- July 3, 2013 label updated for “sprue-like enteropathy”;
- June 13, 2014 ROADMAP update;

- June 27, 2014 lithium interaction added to label;
- September 23, 2014 updates to the dual blockade RAA system and ROADMAP sections of the label;
- February 11, 2016 formatting and editorial changes made to label.

Azor Labeling Updates

- August 7, 2008 added additional information regarding the use of AZOR as add-on therapy to the dosage and administration section;
- May 11, 2009 extended the indication as initial therapy in patients likely to need multiple agents to control their hypertension;
- May 19, 2011 updated post market ADRs to include anaphylactic reactions, peripheral edema, and diarrhea; label also updated to include more information on nonsteroidal anti-inflammatory drug interactions;
- November 2, 2011 drug: drug interaction update for simvastatin;
- November 14, 2011 label edited to clarify the benefits of lowering blood pressure;
- January 18, 2012 fetal toxicity added as black box warning;
- September 28, 2012 aliskiren contraindicated in diabetics and dual blockade of RAA system updated;
- December 11, 2012 drug:drug interaction with colesevelam;
- July 3, 2013 “sprue like enteropathy” added to label;
- June 13, 2014 ROADMAP data added to label;
- July 2, 2014 drug: drug interaction with lithium;
- September 23, 2014 updated areas of ROADMAP and dual RAA system;
- November 1, 2016 updated hyperkalemia as post-market adverse event.

Tribenzor Labeling Updates

- March 25, 2011 myopia and glaucoma added to Warnings/Precautions; drug interaction with nonsteroidal anti-inflammatory drugs added; anaphylactic reactions, peripheral edema, and diarrhea added to the post-marketing section of the label;
- June 21, 2011 labeling supplement to address the benefits of lowering blood pressure and the nonsteroidal interaction section was also updated with edits;
- November 1,2011 simvastatin drug interaction was updated;
- January 19, 2012 fetal toxicity (boxed warning) added;
- September 28, 2012 addressed the aliskiren interaction in diabetic patients; (contraindicated) and added the RAA updates;
- December 10, 2012 colesevelam interaction;
- July 3, 2013 “sprue-like enteropathy” added to label;
- June 13, 2014 ROADMAP data were added to label;
- June 27, 2014 lithium interaction was added to label;
- September 23, 2014 edits to ROADMAP and RAA sections of the label;
- November 1, 2016 hyperkalemia added as post-market adverse drug reaction.

Collectively, these actions demonstrate that DSI was actively engaged with FDA in evolving the labeling for its olmesartan products after their initial introduction into the market. DSI was willing to evaluate new information as it became available and to request and secure FDA approval of labeling changes to ensure that the olmesartan product labels remained adequate and appropriate to ensure safe use.

TIMELINE REGARDING POST-MARKETING GI EVENTS ASSOCIATED WITH OLMESARTAN

The timeline below summarizes the post-marketing information available to Daiichi Sankyo related to reports of celiac disease and other gastrointestinal events reported with olmesartan and the actions taken in response to that information.

From the time of initial approval of Benicar in 2002 through April of 2009, there were sporadic post-marketing reports of gastrointestinal side effects reported with olmesartan. However, these reports were rare and often confounded with other conditions, including in some cases, celiac disease. Original approved labeling for Benicar and Benicar HCT included various GI adverse events and in July of 2005, the labels were updated to include vomiting as a reported adverse reaction. Based on the clinical trial experience with olmesartan, and as reflected in the labeling, some GI events were to be expected in association with the use of olmesartan products.

Beginning in May of 2009, DSI noted six cases of celiac disease reported with Benicar over a ten-day period. DSI submitted an annual Periodic Adverse Drug Experience Report (PADER) to the FDA that described these celiac disease adverse events. By June of 2009 DSI had identified a total of 37 post-marketing cases that mentioned celiac disease either as part of the current or as part of the past medical history and these were under review. During this same time frame, DSI was also actively investigating the presence of gluten in their olmesartan products since gluten consumption is recognized as playing a role in celiac disease. The company was ultimately able to confirm that its products did not contain any gluten.

In November of 2009 a DSI internal report summarized that an increasing number of either new or worsening celiac disease adverse events had been observed with Benicar or Benicar-HCT. The report summarized the status of available reports from time of approval through July of 2009 for each product. A total of 39 cases were retrieved, of which 38 were reported spontaneously post-market, and one from a clinical study done post-approval. Some of the cases were serious while others were non-serious. The majority of the cases (33) reported new celiac diagnoses, while 6 cases reported an aggravation of the pre-existing disease. In 13 of the 39 reports, the purpose of the contact had been to inquire about the gluten content of Benicar. Many of the cases lacked critical details, and many of the patients had tolerated their olmesartan therapy well for years prior to reporting GI symptoms. A literature search conducted by DSI revealed no case reports of celiac disease or gluten sensitivity for olmesartan or other ARBs. DSI additionally noted that there was no known mechanism of action for how olmesartan would lead to the development of celiac disease. The report recommended further investigation of the issue (including possibly a look at the clinical data base or epidemiologic studies) to more fully understand the association with olmesartan. The Company continued to further investigate the issue, including by examining its clinical trial data. At the same time, DSI was conducting a large randomized, long-term, controlled clinical trial called ROADMAP, from which the company was collecting and analyzing adverse event data.

On November 23, 2009, the FDA requested a safety analysis of cases of celiac disease based on their review of DSI's last periodic report. DSI internally reviewed the FDA AERS database during November of 2009. As per a December 16, 2009 email, it was noted that for the ARB class involving 7 drugs, 21 cases of celiac disease were reported, of which 20 were reported with olmesartan. A look at other drugs was also undertaken, including 13 drugs aside from olmesartan. Although olmesartan was noted to have a high PRR (proportional reporting ratio) for celiac disease, two other agents (cetirizine and pantoprazole) had similarly high PRRs. Despite its high PRR, cetirizine is not labeled for celiac disease, and is available over-the-counter. Pantoprazole, which also had a high PRR, is not labeled for celiac disease, even as a post-marketing adverse event. A high PRR alone is not supportive of a drug-associated risk or a labeling change.

On January 14, 2010, DSI submitted its safety analysis in response to FDA's November 23, 2009 request. Based on its review of 43 cases of celiac disease reported globally in association with the use of olmesartan products, DSI concluded that a causal association between exposure to olmesartan medoxomil and celiac disease was very unlikely. Specifically noted by DSI was the fact that there was no gluten present in any of the products; there were no cases of new-onset celiac disease reported in clinical trials involving in excess of 22,000 patients and only one case of a recurrence of celiac disease in a clinical trial patient; all cases of celiac were from the US with one exception from Australia, an unusual geographic distribution for a drug-related adverse event; most of the cases were reported by consumers themselves and not by healthcare providers and were not of high quality; clear biopsy proven evidence of celiac disease was present in only 8 of the 37 newly diagnosed cases; there was no consistent pattern of exposure prior to the celiac event (in fact it was often quite delayed, being longer than a year in 25 of the cases); treatment was discontinued in 29 of the cases and was resumed in 17 cases, with a recurrence of symptoms (but not definitive celiac disease) in 16 of those 17 cases.

DSI noted that the prescribing information for the olmesartan products specifically listed gastrointestinal adverse events including diarrhea, abdominal pain, dyspepsia, gastroenteritis, or nausea and that this could explain the reports of exacerbation of GI symptoms in patients presenting with celiac disease that might not have been formally diagnosed yet. DSI felt that this might also explain why certain patients experienced a recurrence of symptom after resuming treatment. DSI stated that it would continue to monitor all cases of celiac disease reported with olmesartan.

An additional theory considered by DSI in the 2009-2010 timeframe was the possibility that some of the celiac cases observed in association olmesartan may have arisen from patients following what was known as the "Marshall Protocol." The Marshall Protocol recommended that patients take, among other medications, Benicar 40 mg four times a day to address underlying inflammatory autoimmune disease.[17] The protocol began in 2002 and gained in popularity in the US for the treatment of a variety of autoimmune conditions, including sarcoidosis, rheumatoid arthritis, and chronic fatigue syndrome. Other ARBs were not recommended by the Marshall Protocol, only olmesartan was posited to work, based on its putative ability to activate the Vitamin D receptor. If patients with autoimmune disorders were taking olmesartan preferentially, it might explain the increased reports of celiac disease (an immune mediated condition itself) unique to olmesartan.

[17] https://mpkb.org/home/mp

In April of 2010, an article was published by Rubio-Tapia et al in Clinical Gastroenterology and Hepatology, volume 8, pages 344-349. The article was entitled: "Gluten-Free Diet and Steroid Treatment are Effective Therapy for Most Patients with Collagenous Sprue." The article reviewed thirty patients with celiac disease and discussed their clinical characteristics, histologic findings, treatment and prognosis. The article discussed medication risk factors that they noted with acetylsalicylic acid or nonsteroidal anti-inflammatory drug therapy taken by one third of their patients. For these drugs, the authors observed "the effect that these drugs might have in exacerbations and/or progression of intestinal injury is unknown but deserves consideration." The consumption of one or more drugs associated with microscopic colitis was observed in 47% of their celiac disease patients. The authors noted that pro-inflammatory or pro-fibrotic drugs may be related to celiac disease as well as microscopic colitis, although this remained unknown. Indeed, in contrast to pro-fibrotic drugs, the authors noted that one third of their patients were taking olmesartan, a drug with anti-fibrotic properties outside the GI tract. The authors did not propose any connection between olmesartan and celiac disease.

One of the co-authors of the aforementioned 2010 Rubio-Tapia publication was Dr. Joseph Murray. In May of 2009, Dr. Murray had apparently contacted DSI and asked if there was any information on GI side effects and Benicar. DSI called Dr. Murray back and left a message with his receptionist. Dr. Murray contacted DSI a second time on November 26, 2010 to discuss possible side effects of olmesartan and a "rare enteropathy." It was noted he "may have seen several cases that would suggest association with this and the use of olmesartan." DSI tried to reach Dr. Murray on November 29, 2010 but he was not available. A message was left with his office and DSI further followed-up with letters on December 1 and December 30, 2010. On January 26, 2011 DSI received a faxed letter from Dr. Murray stating his interest in discussing "a possible association between Benicar and enteropathy." He apologized for the difficulty in reaching him and noted that he had five patients who had an enteropathy-like disease and were taking olmesartan. He suggested arranging a time for a teleconference. DSI telephoned Dr. Murray on February 11, 2011 but was again unable to speak with him.

As part of DSI's ongoing evaluation of the celiac disease issue, in May of 2010, it further investigated whether there were any cases of celiac disease reported in a recently completed study called ROADMAP (Randomized Olmesartan and Diabetes Microalbuminuria Prevention). This study enrolled 4512 Type 2 diabetic patients of whom 4449 were randomized to treatment. Approximately half the patients were randomized to placebo (n=2215) versus half who received olmesartan 40 mg once daily (n=2232) with the key objective to compare the time to first occurrence of adjudicated microalbuminuria. Secondary objectives of ROADMAP were to assess cardiovascular events, including CV mortality, renal function, and retinopathy. The study was planned to conclude when 326 microalbuminuria events had been reported. The average duration of follow-up in the ROADMAP study was 3.3 years. ROADMAP therefore provided an extensive and long term randomized placebo controlled database.

Safety findings related to the GI system during the double-blind randomized phase of ROADMAP were unrevealing of celiac disease or any GI safety signal. Table 12.4 of the clinical study report conveys that 11.6% of olmesartan treated patients experienced adverse events related to the gastrointestinal system versus 12.3% of placebo treated patients. Table 12.5 conveys the most common adverse events arising in at least 2% or more of patients in either treatment group. Diarrhea was the only GI event that made this cutoff, being observed in 2.3% of patients in each treatment arm. An evaluation of severe adverse events arising in at least 4 patients within each treatment arm also provided no evidence for a GI signal of concern, as no severe GI events were listed. Finally, serious adverse events reported by at least 2

patients or more in either treatment group were listed in Table 12.10, and here the only GI events listed were appendicitis (2 olmesartan subjects and 3 placebo subjects), gastric cancer (1 olmesartan subject and 3 placebo subjects), and abdominal pain (3 olmesartan subjects versus 0 placebo subjects). One patient in ROADMAP experienced an SAE of gastroenteritis with hypokalemia after taking olmesartan for approximately 10 months. ROADMAP provided no evidence of a serious GI safety concern or celiac disease in association with olmesartan after following over 4000 patients (evenly randomized) for a mean of 3.3 years.

In July of 2010, FDA approved Tribenzor without any labeling for celiac disease or enteropathy. If the Agency felt that celiac disease or some other type of GI disorder needed to be added to the labeling of olmesartan products, they could have (and would have) implemented a change at that time. The FDA continued to follow the side effect profile of olmesartan carefully, but they did not change the label or even initiate a TSI (Trackable Safety Issue) at this time.

On September 1, 2010, a Signal Detection Report for olmesartan was completed within DSI based on a review of adverse events collected from January 1st to June 30th, 2010. The report covered adverse reports that were more recently reported (first and second quarter of 2010) and also more comprehensively from April 2002 to second quarter 2010. Reporting ratios of 2% or higher were noted for diarrhea, nausea, drug ineffective, fatigue, edema, increased blood pressure, myalgia, dizziness, headache, cough, pruritus, rash, and hypotension. The company concluded that these events required further investigation. A November 8, 2010 DSI analysis concluded that although diarrhea and peripheral edema were currently labeled for all olmesartan products marketed in each global region, it was recommended to add “diarrhea” and “peripheral edema” to the Company Core Data Sheet. On November 30, 2010, all core data sheets for olmesartan products were updated.

At a Pediatric Advisory Meeting held on January 30, 2011, the FDA discussed the experience of Benicar in hypertensive children ages 6 to 17 years of age. (Benicar had been previously approved for pediatric use by the FDA on February 4, 2010). This was a pediatric meeting focused on the safety of Benicar. The FDA slide presentation for this meeting (slide 12, presentation by Dr. Nadia Hejazi of FDA) noted: “There were no relevant differences between the adverse events profile for pediatric patients and that reported for adults.” No new safety signals were identified and no concerns were raised at this meeting regarding celiac disease or GI adverse events. The FDA asked the committee if continued routine safety monitoring was appropriate and the panel unanimously agreed with that approach. Despite full knowledge of the existence of post-marketing reports of celiac disease with olmesartan, the Agency did not raise any concerns at this meeting regarding celiac disease or the GI safety profile of olmesartan in either pediatric patients or adult patients with hypertension.

In February of 2011, DSI submitted Changes Being Effected (CBE) notifications to the FDA to add diarrhea as an adverse event in the post-marketing experience section for the olmesartan combination products. The company informed FDA that it did not intend to add diarrhea to the post-marketing section for Benicar because this was already described as an adverse event for the product. By May of 2011, the FDA had approved all of three supplements, including adding diarrhea to the post-marketing section, without requiring any other updates. Although it had full authority to do so, the FDA did not require additional studies or mandate labeling changes to address the potential association between olmesartan and celiac disease or enteropathy, or any serious GI disorder. Nor did the FDA make DSI

aware that it had identified any specific safety signal from its own database and review of the olmesartan products.

In January of 2012, DSI was notified by the FDA that olmesartan, as well as most other members of the ARB class, were the subject of an inquiry within the FDA's "Mini-Sentinel" program involving the diagnosis of celiac disease. Mini-Sentinel is an FDA program designed to identify potential drug safety issues through a system of linked healthcare databases in the United States. This was the first notification to DSI that such a review had been undertaken by the FDA in connection with olmesartan.

On January 18, 2012 the results of the Mini-Sentinel query were released. Findings revealed very low rates of celiac disease for all 7 ARB agents with no appreciable difference between olmesartan and the other ARBs. The FDA's impression as of January 2012 was that the Mini-Sentinel system did not support a unique olmesartan-celiac association. According to a report in the "Pink Sheet" on January 23, 2012, the Mini-Sentinel program was utilized to examine the reported connection between ARBs and celiac disease. Dr. Bob Temple (of the FDA) noted that the drug linked most often to celiac disease in the original reports, i.e. olmesartan, "was not the drug with the highest incidence of the disease in the Mini-Sentinel analysis." Dr. Temple is further quoted as saying "it now appears that the drug that was singled out [Benicar] didn't look any different from anything else, and that's reassuring."

On June 21, 2012, the Mayo Clinic issued a press release to announce the publication of a report in the Mayo Clinic Proceedings, "Severe Spruelike Enteropathy Associated With Olmesartan," (Mayo Clin Proc August 2012; 87(8):732-738), addressing a potential "association" between olmesartan and severe GI disorders such as nausea, vomiting, diarrhea, and weight loss – symptoms common among those with celiac disease. The report included detailed information on 22 patients who had been treated with olmesartan (mean duration 3.1 years), and then developed GI symptoms of diarrhea, weight loss, nausea, vomiting, or abdominal pain. Patients were tested for antibodies for celiac disease, but these were negative, yet they all had intestinal biopsies that were consistent with celiac sprue, showing villous atrophy and varying degrees of mucosal inflammation. Colonoscopy was done in 13 patients with microscopic colitis found in 5 patients. The patients had undergone varying treatments for their GI symptoms, but upon cessation olmesartan, a positive clinical response was shown, and in 17 patients, histologic recovery of the duodenum was observed. The case series and full sets of clinical information provided the first evidence of a "novel association" between olmesartan and what was characterized as "sprue-like enteropathy." As per the authors' own conclusions, the case series, while supporting an association, lacked the information necessary to prove causality.

Upon learning about the Mayo case series, DSI immediately began to gather all the information it could on the 22 patients. Emails within the company expressly noted that they were dealing with what appeared to be a "new diagnosis" and that the focus was no longer on celiac disease but on the newly described condition: "sprue-like enteropathy." DSI reached out directly to Dr. Joseph Murray (the lead author on the Mayo case series) on multiple occasions to assist in the information gathering process. As documented in an email dated June 27, 2012, Dr. Murray confirmed that the Mayo team did not consider their findings to be an indication of causality, only an association.[18] He further characterized

[18] Dr. Murray later re-confirmed that there was no proof of "cause and effect" in a video presentation uploaded on YouTube on October 15, 2012. See https://www.youtube.com/watch?v=CmrZBeikR-Y

the disease process as "very particular and very peculiar" and that their identification of this "very rare" association was likely a consequence of Mayo's status as a "tertiary/quaternary" medical center. On June 29, 2012 DSI was notified by FDA that a DARRTS Trackable Safety Issue (TSI) had been created on June 22, 2012 for olmesartan.

On July 11, 2012 the FDA, noting the recent Mayo case series, requested that DSI provide a review of all serious spontaneous reports of malabsorption, enteropathy, microscopic colitis, celiac or sprue like symptoms or chronic diarrhea with clinically significant weight loss associated with olmesartan. The FDA requested that any mechanism of action or contributing factors for this be provided. Identical requests were directed to the sponsors of other ARB medications. The FDA requested that this information be provided within 60 days. DSI immediately held joint meetings with various members of its team to address their action plan. An updated analysis of olmesartan clinical study databases and a review of relevant preclinical results would be provided. Potential mechanism of action would also be addressed as well as consideration of the ROADMAP study (large, randomized, and long term, placebo-controlled) which had shown no association between olmesartan and intestinal side effects. DSI continued throughout this time frame to gather additional information from Dr. Murray and his colleagues on the 22 patients included in their case series.

During this same time period, Drs. Jan Menne and Hermann Haller, investigators of the ROADMAP study, submitted a Letter to the Editor of the Mayo Clinic Proceedings. They noted that in more than 2200 patients taking high-dose olmesartan for more than 3 years they did not observe any intestinal adverse effect signal. They shared a table describing gastrointestinal adverse events (including fatigue and weight loss as well as other events) reported in ROADMAP with similar and balanced incidences between olmesartan and placebo treatment arms. The authors concluded that while they could not rule out the possibility that a "sprue-like enteropathy" might be associated with olmesartan, their data from ROADMAP "did not identify a link between olmesartan use and the occurrence of gastrointestinal disease."[19]

DSI formally responded to FDA's prior information request on September 28, 2012. Key points were:

- A total of 80 cases from the global safety database since the approval of Benicar in 2002 related to malabsorption, enteropathy, microscopic colitis, celiac or sprue-like symptoms, or chronic diarrhea with clinically significant weight loss were found;
    - None of the cases were deaths or life –threatening;
    - Hospitalization was needed in 55 of the 80 cases (69%);
    - 22 of the cases were the ones reported in the Rubio-Tapia article;
    - 58 were spontaneous reports that were not part of the Rubio-Tapia article;
        - 41 of the 58 reports were for celiac disease, with the majority (78%) reported by patients;
        - The remaining 17 of the 58 reports were for diarrhea, significant weight loss (12), malabsorption (1), and microscopic colitis (4);

[19] This Letter to the Editor was subsequently published in the Mayo Clinic Proceedings in December of 2012.

- Most of the cases were from consumers which compromised the robustness and utility of the dataset (often missing key information);
- The DSI global safety database did not substantiate the association of olmesartan with sprue-like illness as described in the Mayo case series publication. There was one case reported a follow-up endoscopy with resolution of the intestinal villous atrophy (17 days after the last dose of olmesartan), but this case involved a number of other medications including a statin, dexlansoprazole, and antibiotics;
- The DSI global safety database did reveal cases of positive rechallenge (28 cases were described, some with a single rechallenge, some with 2-3 rechallenges, and one case had 3-4 rechallenges), but often the timing of symptoms was within the same day or even within hours of re-starting olmesartan and this was not considered consistent with a pathology of recurrent villous atrophy or microscopic colitis as described in the Mayo Case series; the DSI cases and their rapid effect upon rechallenge suggest possibly "more consistent with an allergic process in a small, select group of patients";
- The DSI global database indicated that "any possible, serious, olmesartan-induced enteropathy is rare, nonfatal, and reversible;" and this was also observed in the Mayo case series;
- The event rate reporting by year began with 4 reports in 2006, 2007, and 2008. In 2009, 17 cases were noted, with 14 in 2010, 9 in 2011, and 28 (22 of which were from the Mayo Clinic) in 2012.
- The report also addressed preclinical findings, noting no GI toxicity in 1 year rat and dog studies, and no findings of villous atrophy or microscopic colitis in a 2-year rat carcinogenicity study.

Based on its assessment, DSI recommended no change to the label. DSI awaited the FDA's response and continued to study the GI issue. In November of 2012, DSI conducted a further detailed literature review concerning "sprue-like enteropathy" and also consulted with external experts during this time frame. DSI also expected to receive additional insights once the FDA had the opportunity to review the data which had been requested from all the ARB sponsors.

On April 18, 2013, DSI was contacted by the FDA with reference to scheduling a telephone conference to discuss "labeling changes to your olmesartan products, based on the information that we have about malabsorption/sprue like disease in some patients treated with olmesartan." FDA informed DSI that the labeling changes would only be for olmesartan and not for the other ARBs. DSI began to prepare for this call and asked the FDA to provide additional details on the analyses that the agency had performed to reach its conclusion that a labeling change was warranted. The telephone conference was scheduled for May 8, 2013.

On May 6, 2013, the FDA provided DSI with the language it wanted to incorporate into the olmesartan label:

> WARNINGS AND PRECAUTIONS
>
> **Sprue-like enteropathy.** Severe, chronic diarrhea with substantial weight loss has been reported in patients taking olmesartan months to years after drug initiation. Intestinal biopsies of patients often demonstrated villous atrophy. If a patient develops these symptoms during treatment with olmesartan, exclude other etiologies. Consider discontinuation of olmesartan in cases where no etiology is identified.

On May 7, 2013 DSI responded to the FDA accepting the FDA's language in its entirety but for replacing the word "olmesartan" in the final sentence with the Tradename for the drug. The FDA project manager responded that she was "sure that your proposal will be accepted."

On May 8, 2013, DSI had the teleconference with the FDA. An Executive Summary of the call from DSI confirmed FDA was requesting an update to olmesartan's label and that this "was primarily driven by the spontaneous reports with supportive data from the Mini-Sentinel." It was noted that in the Mini-Sentinel, the FDA had re-assessed the GI safety signal by requiring ARB use for longer than 12 months, and longer than 24 months. In re-evaluating the data in this way, olmesartan had a "pattern of increased risk." FDA noted they would make the results of Mini-Sentinel publically available and that an FDA Drug Safety Communication would be issued to coincide with the updated olmesartan labels. DSI agreed to submit revised labeling for olmesartan products as Changes Being Effected (CBE) 30-day submissions within 2-3 weeks.

Further details concerning the FDA's assessment of the GI safety signal associated with the ARB class can be found in the FDA's Trackable Safety Issue (TSI) Integrated Review Memorandum dated May 14, 2013. A table in this memorandum detailed the materials reviewed by the FDA which included:

- A pharmacovigilance review of malabsorption with olmesartan by Eileen Wu dated 11/30/11
- The Rubio-Tapia case series, dated 6/25/12
- A consultative review of information submitted by sponsors of ARBs by Zana Marks dated 3/26/13
- The Mini-Sentinel study results by Marsha Reichman, in a review dated 5/7/13
- A GI consultative review from Thomas Papoian, to review potential mechanisms, dated 3/14/13
- A drug utilization review by Grace Chai dated 6/6/11.

The FDA's pharmacovigilance review of malabsorption with olmesartan in the TSI Review Memorandum, identified 23 cases, some of which were also reported by Rubio-Tapia. The FDA had searched the medical literature and did not find any additional reports of olmesartan associated diarrhea, villous atrophy, malabsorption, or celiac disease.

The FDA noted that both the Rubio-Tapia article and the FDA FAERS case series (i.e. the post-marketing reports) had described a sprue-like enteropathy condition characterized by late-onset chronic diarrhea and weight loss. With a 1-year and 2-year minimum exposure, the signal was strongest with olmesartan. It was observed also that in the Rubio-Tapia article there were cases of de-challenge with improved histology (not just improved symptoms).

The gastroenterology consultative review in the TSI Review Memorandum noted that the sponsors for the 7 ARBs other than olmesartan had not found an association between each ARB and sprue-like enteropathy, and none of these sponsors recommended labeling changes. A considerable number of reports were confounded by other possible causes, and had lack of sufficient information. As for olmesartan, the sponsor (DSI) had identified 80 cases in their global safety database (including 22 cases from the Rubio-Tapia publication). The gastroenterology reviewer concluded that "although the olmesartan sponsor's safety database did not identify a signal for enteropathy, the Rubio-Tapia case series provides convincing evidence of an association between olmesartan and a sprue-like enteropathy."

The Mini-Sentinel and CMS Medicare Database evaluations performed by the FDA were depicted in Figures 1 and 2 of the TSI Review Memorandum. The figures describe the number of new events per 1 million days of drug treatment by various products. For the Mini-Sentinel Figure 1, the number of events with olmesartan versus other 7 other anti-hypertensive agents (4 ARBs and 3 non-ARBs), were similar when there was no consideration of the length of use. In fact, Valsartan had the greatest rate of events, slightly over 2 events per million days at risk. When the FDA evaluated the same risk, but required at least a year of treatment, irbesartan had the greatest risk (1.4 events per million days of use), with olmesartan coming in second (at 1.0 events per million days of use). Only when the requirement was for at least two years of treatment was olmesartan's risk the greatest: 1.1 events per million days at risk, compared to the other agents where the risk ranged from 0.0 to 0.6 events/million days at risk.

For the CMS Medicare Database outlined in Figure 2, the number of new events of celiac disease in association with olmesartan (without restriction for duration of use) was very similar to that of other ARBs. However, upon requiring at least 1 or 2 years exposure, olmesartan had a higher rate (slightly above 4 events per million days of use) versus the other ARBS, (which had 2-3 events per million days of use). FDA noted that for both the Mini-Sentinel and CMS Medicare Database, the interpretation of the data was limited by a small number of overall events over prolonged exposure periods.

At the end of its TSI review and analysis, the FDA did not conclude that olmesartan causes sprue-like enteropathy. Rather, as noted in the TSI Memorandum, the FDA team found "sufficient evidence to support a safety signal of olmesartan and sprue-like enteropathy and recommended that olmesartan's labeling should be amended to address this risk." The FDA team proposed labeling updates with an FDA Drug Safety Communication to inform health care professionals.

On May 31, 2013, Changes Being Effected (CBE) notifications were submitted by DSI with the FDA recommended text for sprue-like enteropathy for all olmesartan products. These were approved by the FDA on July 3, 2013 to include new text in the Highlights/Warnings and Precautions section of the Benicar label as follows:

> Sprue-like enteropathy has been reported. Consider discontinuation of Benicar in cases where no other etiology is found (5.5).

Under Warnings and Precautions the following was added:

5.5 Sprue-like Enteropathy

Severe, chronic diarrhea with substantial weight loss has been reported in patients taking olmesartan months to years after drug initiation. Intestinal biopsies of patients often demonstrated villous atrophy. If a patient develops these symptoms during treatment with olmesartan, exclude other etiologies. Consider discontinuation of Benicar in cases where no other etiology is identified.

Under Adverse Reactions/Postmarketing Experience, the following text was added:

Gastrointestinal: Vomiting, sprue-like enteropathy.

Consistent with the TSI findings and memorandum, the FDA-proposed and approved labeling did not state that olmesartan causes sprue-like enteropathy. Instead, it noted that diarrhea with weight loss "has been reported in patients taking olmesartan. . . ." When the FDA believes that a medicine can cause an adverse event, it mandates or approves labeling that says so. For example, the 2002 launch label for Benicar contains a Boxed Warning concerning fetal morbidity and mortality that states: "**[D]rugs that act directly on the renin-antiogensin system (like Benicar)** ***can cause injury and even death to the developing fetus*****.**"[20] The FDA-approved label reflects the Agency's medical conclusions regarding the risks and benefits of the medicine.

Also on July 3, 2013, the FDA issued a Drug Safety Communication to make the public aware of the labeling changes. The Communication does not reflect the FDA's medical conclusions regarding the benefits and risks of olmesartan. Rather, the FDA's conclusions regarding the safety profile of olmesartan (and all FDA-approved medications) are reflected in the product labeling approved by FDA.

REVIEW OF DR. KESSLER'S REPORT

I've reviewed Dr. Kessler's November 30, 2016 Expert Report. I disagree with many of his opinions. I address below his opinion that de/rechallenge meets the FDA standard for reasonable evidence of a causal association and his opinion that DSI should have recognized the existence of a non-celiac serious GI disorder from post-marketing adverse event reports prior to June of 2012. To the extent that Dr. Kessler expresses other opinions in his report that are contrary or inconsistent with the conclusions I reach throughout my expert report, I disagree with those opinions as well.

De/Rechallenge Evidence and "reasonable evidence of a causal association"

In his report, Dr. Kessler notes that 21CFR 201.57(c)(6) requires the Warning/Precaution section of a medication's labeling to be revised to include a warning about a clinically significant hazard "as soon as there is a reasonable evidence of a causal association; a definitive causal relationship need not be established . . ." He then focuses on certain post-marketing adverse event reports for olmesartan from the 2006-2007 timeframe which he suggests "showed reproducible positive rechallenge cases, thus satisfying the FDA standard of "reasonable evidence of a casual association.""[21] I disagree with Dr. Kessler.

The determination of whether reasonable evidence of a causal association exists to warrant a labelling change is a complex medical judgment undertaken by medical experts at the sponsoring pharmaceutical company and the FDA. While positive dechallenge and rechallenge experience can be a factor in determining if there is reasonable evidence of a causal association between an adverse event and a suspect drug, it is but one of many factors. Those other factors include:

- The frequency of reporting of the event;
- Whether the adverse event rate in the drug treatment group exceeds the rate in the placebo and active-control group in controlled trials;
- Evidence of a dose-response relationship;

[20] Benicar Launch Label, 2002 (bold emphasis in original).

[21] Kessler report, p 2.

- The extent to which the adverse event is consistent with the pharmacology of the drug;
- The temporal association between drug administration and the event; and
- Whether the adverse event is known to be caused by related drugs.[22]

Consideration of all these factors is not a simple matter of box-checking. Indeed, as the FDA Guidance for the Adverse Reactions section of the labeling notes: "Decisions on whether there is some basis to believe there is a causal relationship are a matter of judgment and are based on factors such as (the ones cited above)."[23] The Guidance further states:

> (T)he Agency emphasizes that reviewer and applicant judgment remain critical in assessing how or whether to present information on an adverse reaction. FDA reviewers and applicants should assess such factors as seriousness, severity, frequency, and strength of causal association in determining which adverse reactions to include in the ADVERSE REACTIONS section and in characterizing those reactions. In general, the ADVERSE REACTIONS section includes only information that would be useful to health care practitioners making treatment decisions and monitoring and advising patients. Exhaustive lists of every reported adverse event, including those that are infrequent and minor, commonly observed in the absence of drug therapy or not plausibly related to drug therapy should be avoided (see § 201.57(c)(7) and the Glossary at the end of this guidance for a definition of Adverse Reaction). Such lists are not informative and tend to obscure the more clinically meaningful information.[24]

Moreover, the 2005 FDA Guidance on Good Pharmacovigilance Practices cited by Dr. Kessler does not state that dechallenge and rechallenge evidence demonstrates reasonable evidence of a causal association. Rather, the Guidance focuses on such evidence as supportive of a safety signal, necessitating further assessment:

> Pharmacovigilance principally involves the identification and evaluation of safety signals. In this guidance document, safety signal refers to a concern about an excess of adverse events compared to what would be expected to be associated with a product's use. Signals can arise from postmarketing data and other sources, such as preclinical data and events associated with other products in the same pharmacologic class. It is possible that even a single well-documented case report can be viewed as a signal, particularly if the report describes a positive rechallenge or if the event is extremely rare in the absence of drug use. *Signals generally indicate the need for further investigation, which may or may not lead to the conclusion that the*

[22] Guidance for Industry: Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format, October 2011, p. 3.

[23] Guidance for Industry: Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products – Content and Format, January 2006, p. 8 (emphasis added).

[24] *Id.* at 1-2.

product caused the event. After a signal is identified, it should be further assessed to determine whether it represents a potential safety risk and whether other action should be taken.[25]

The 2005 Guidance, similar to the labeling guidances previously cited, states that evaluating whether a causal relationship between the use of a product and an adverse event exists requires an assessment of the following:

- Occurrence of the adverse event in the expected time;
- Absence of symptoms related to the event prior to exposure;
- Consistency of the event with the established pharmacological/toxicological effects of the product;
- Consistency of the event with the known effects of other products in the class;
- Existence of other supporting evidence from preclinical studies, clinical trials, and/or pharmacoepidemiological studies; and
- Absence of alternative explanations for the event (e.g., no concomitant medications that could contribute to the event; no co- or pre-morbid medial conditions.[26]

Safety information in medicine labeling is, as noted above, a summary of the information essential to allow for the safe use of the drug. There is not a simple, formulaic approach to determine what information does and does not get included in labeling. To say in isolation that positive de/rechallenge evidence that is reproducible *per se* meets the FDA standard of reasonable evidence of a causal association is incorrect. The many FDA guidances on evaluating reported adverse events to determine if there is reasonable evidence of a causal association thus describe a complex set of criteria to be considered and evaluated through the medical judgment of the pharmaceutical company and the FDA to make a determination if labeling of that event is warranted or appropriate. Consistent with the FDA's guidance, DSI's Standard Operating Procedures ("SOPs"), as discussed by Dr. Kessler in his report, identifies rechallenge evidence as one of numerous factors to consider and evaluate in assessing causality.

The examples cited by Dr. Kessler in which the FDA purportedly changed drug labeling based on dechallenge and rechallenge evidence only further highlight that, contrary to his opinion, the FDA typically takes into account multiple and diverse data points when concluding a labeling update is warranted. Factors other than positive dechallenge and rechallenge experience that the FDA took into account in these cases included:

- Temporal relationship with detailed clinical descriptions;
- The nature of the adverse event itself (rare adverse events that are not often confounded by other conditions or medications versus common adverse events that are confounded by other conditions or medications);
- Relevant laboratory data;
- Physician substantiated diagnoses;

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[25] Guidance for Industry: Good Pharmacovigilance and Pharmacoepidemiologic Assessment, March 2005, p 4 (emphasis added).

[26] Guidance for Industry: Good Pharmacovigilance and Pharmacoepidemiologic Assessment, March 2005, pp. 6-7.

- Skin biopsy confirmation;
- Liver biopsy confirmation;
- Concomitant medications with similar adverse reaction profiles;
- Evidence of a dose response relationship;
- Autopsy results;
- X-ray results;
- Cat scan results:
- Cerebrospinal fluid analysis; and
- Tissue and fluid cultures for the presence of infectious organisms.

Even with positive rechallenge data, FDA could not uniformly make a clear determination of reasonable evidence of a causal association in each case. For example, with regards to the reports of hearing loss in patients taking PDE5 inhibitors (the Viagra, Revatio, Levitra, and Cialis case cited by Dr. Kessler[27]), FDA noted that "In many cases, medical conditions and other factors may have contributed to the adverse event," and, "there was limited follow-up information for these post-marketing case reports, making it difficult to determine whether these reports were directly related to the use of a PDE5 inhibitor, and underlying medical condition, or other risk factors for hearing loss, a combination of these factors, or other factors."[28]

For Provigil,[29] only 1 of the 6 cited reports of severe skin adverse events, including Stevens-Johnson Syndrome, a rare event that is routinely recognized as an event that is drug-induced as opposed to naturally occurring, included positive rechallenge data, but even that case was confounded by the fact that the patient also received therapy with Lactimal, a drug product with a labeled Warning for Stevens-Johnson Syndrome.[30]

For the Tumor Necrosis Factor-alpha Blockers (Remicade, Enbrel, Humira, Cimizia, Simponi),[31] only 1 of the 129 cited reports of opportunistic infections included positive rechallenge experience, but even that case was uncertain, "because L. pneumophila was not found in cultures during the second episode, we could not determine whether the infection was due to a new environmental contamination or to the intracellular persistence of the bacteria."[32]

Thus, in deciding to revise the product labeling in the cases cited by Dr. Kessler, the FDA considered many factors and made its decision based on the totality of evidence. To the extent rechallenge data

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[27] Kessler report, pp. 18 – 19.

[28] Winter 2008 Drug Safety Newsletter, Volume 1, No. 2.

[29] Kessler report, pp 16 – 17.

[30] Fall 2007 Drug Safety Newsletter.

[31] Kessler report, pp 20 – 21.

[32] Tubach, F., et. al., Emergence of Legionella pneumophilia pneumonia in patients receiving tumor necrosis factor alpha antagonists. Clin Infectious Disease, 2006; 43: e95-100.

was even a part of the FDA's calculus in concluding a labelling update was warranted, it was just one of many factors contributing to that decision.

Interpretation of Post-Marketing Adverse Event Reports

Dr. Kessler's report outlines a methodological review of 62 MedWatch forms that were submitted to the FDA concerning olmesartan that met the following criteria: 1) at least one of the symptoms of diarrhea, vomiting, or celiac disease appeared in either coded preferred terms (section G.8) or the narrative (section B.5); 2) positive rechallenge documented through either a checked box or the narrative; and 3) seriousness documented through either a checked box in Section B.2 or other evidence of hospitalization.

Dr. Kessler reviewed these reports with the assistance of a gastroenterologist, who concluded that 60 of the 62 cases described a symptomology that was consistent with the novel condition the Mayo case series in June 2012 identified as "sprue-like enteropathy." Notably, diarrhea and vomiting are two ubiquitous adverse event terms associated with sprue-like enteropathy as well as thousands of other conditions.

As an initial matter, it is worth noting again that spontaneous adverse event reports in the post-marketing setting, such as the reports cited by Dr. Kessler, suffer from several limitations. *See Overview of FDA Safety Regulations and Review Practices, above.*

I reviewed the 60 cases. The reports describe an acute onset of GI complaints such as nausea and vomiting or bad diarrhea (or both) that arose in both patients with pre-existing or recently diagnosed celiac disease and in patients with no such diagnosis. The symptoms arose often after patients had been on olmesartan successfully for years. Rechallenge was reported in some cases to result in a recurrence of the symptoms, although it should be noted that most of the reports do not mention whether or not the patient was following a gluten-free diet. Many of the cases of rechallenge (44 of 60), per Dr. Kessler's review, were documented as a box checked indicating rechallenge, while the remainder (16 of 60) contained narratives. As Dr. Kessler notes, rechallenge "is a potentially strong indicator of causality, but interpretation of the results of rechallenge is highly dependent on the natural course of the event being considered. For noncyclical events that are exceedingly rare in the background and that present in clear, objective fashion (e.g. acute liver failure, aplastic anemia, Stevens Johnson Syndrome) recurrence of that same event upon rechallenge supports a potential association with the drug. Even in such cases, however, other factors need to be considered and the totality of data is what drives a labeling decision. For common subjective events that can occur in cyclical or recurrent fashion and that may be due to a multitude of causes, such as diarrhea and vomiting, recurrence of the event upon rechallenge is far less definitive.

The adverse events reported in the 60 reports are events of nausea, vomiting, diarrhea that occur in a cyclical or recurrent fashion, particularly in patients with underlying celiac disease. In addition, many of the 60 reports cited other confounding conditions such as clostridium difficile infection, giardiasis, bacterial colitis, or digestive candidiasis. Thus, these 60 cases, even with rechallenge information, would not support an association of celiac disease or enteropathy with olmesartan, much less a causal link. The cases may, at most, have supported an association between GI side effects and olmesartan, but these were already noted in the label.

Interestingly, in several of the reports, it was noted that the patient (and/or physician) had specifically reported that they did not think olmesartan was responsible for the celiac disease.

To the extent that Dr. Kessler opines that DSI should have (a) concluded that the reports of celiac disease contained within the 60 reports were misdiagnosed by the patient's physician, and then (b) overrode that diagnosis and re-diagnosed those patients as part of the company's pharmacovigilance activities, I disagree. In its Guideline for Postmarketing Reporting of Adverse Drug Experiences, the FDA advises: "The (adverse) reaction should be described in detail using the reporter's own words," and "Use initial reporter's own words; FDA COSTART of other coding may also be added."[33] In addition, in evaluating spontaneous, post-marketing adverse event reports, the FDA relies upon the information as reported to the pharmaceutical company (using standardized using safety terms), and does not consider post-hoc adjudications of the reports as anything more than exploratory in nature.

Dr. Kessler suggests that based on the 60 reports, DSI should have changed its labeling by the end of 2006 and no later than 2007. In 2006 and 2007, as well as at any point from 2007 through 2013 when the FDA requested a labeling update for the olmesartan products to include sprue-like enteropathy, the FDA could have but did not mandate nor request that DSI update its labels to warn of that condition. When the FDA completed its review of the original NDA for Azor in September 2007 and approved that product, or when it reviewed and approved the original NDA for Tribenzor in July 2010, FDA could have but did not suggest a labeled warning for sprue-like enteropathy for either those two products (nor for the other two olmesartan products). When the FDA reviewed DSI's request to update the labeling to add diarrhea to the Post-Marketing Experience subsection of the Adverse Reactions section of the label in early 2011, the FDA could have but did not request that DSI add sprue-like enteropathy to the labels. And when DSI proposed labeling updates for Benicar in September 2007 (S-012), February 2010 (S-018), May 2011 (S-019), June 2011 (S-020), February 2012 (S-021) March 2012 (S-023), September 2012 (S-025) and December 2012 (S-026); for Benicar HCT in November 2007 (S-008), May 2011 (S-013 and 014), January 2012 (S-016), September 2012 (S-020) and December 2012 (S-021); for Azor in August 2008 (S-003), May 2009 (S-002), May 2011 (S-010 and 012), November 2011 (S-014), January 2012 (S-016), September 2012 (S-019) and December 2012 (S-020); or for Tribenzor in March 2011 (S-001), June 2011 (S-003), November 2011 (S-007), January 2012 (S-008), September 2012 (S-001) and December 2012 (S-012), the FDA could have but did not suggest that DSI update its labeling to warn of sprue-like enteropathy.

Between 2006 and 2013, the olmesartan labeling described gastrointestinal adverse reactions including vomiting, diarrhea, nausea, and other events. The labeling did not warn of a potential risk for celiac disease. Importantly, the FDA could have but did not request that DSI update its labels to include a potential risk for celiac disease after DSI submitted its celiac analysis to the FDA in January 2010. To date, there remains no scientific evidence that olmesartan causes celiac disease or exacerbates it; the potential association described in the Mayo case series was for a new/novel entity called "sprue-like enteropathy," where patients are negative for the antibodies to gluten. The FDA, the Mayo case series, and DSI all concluded that there is no evidence that olmesartan causes celiac disease. Thus, to have updated the labels to warn about a potential risk for celiac disease starting in 2006 or 2007 would have been an inaccurate medical statement and misleading to physicians. Such an action would have complicated the diagnosis and treatment of patients reporting gastrointestinal side effects after taking olmesartan products, and may have led to the unnecessary discontinuation of olmesartan products in

[33] Guideline for Postmarketing Reporting of Adverse Drug Experiences, March 1992 – p.21.

patients with celiac disease.

Ultimately, the FDA makes final determination of whether a medicine's product labeling should warn of the potential risk of a certain adverse event. As described in the preamble to the PLR labeling rule, "Under the Act, FDA is the expert Federal public health agency charged by Congress with ensuring that drugs are safe and effective, and that their labeling adequately informs users of the risks and benefits of the product and is truthful and not misleading," and "In fact, the determination whether labeling revisions are necessary is, in the end, squarely and solely FDA's under the act."[34]

The safety information in the FDA-approved labeling reflects the FDA's assessment and evaluation of the sponsor's submitted clinical data, the sponsor's evaluation of those data, the determination of the frequency of the occurrence of the adverse reactions (not the establishment of a definitive causality), and the sponsor's proposed labeling. In the course of that assessment and evaluation by the FDA, there may be a dialogue and a sharing of opinions between the sponsor and FDA in what is typically a collegial process. But, at the end of that process, the FDA has the ultimate authority and makes the final decision on the content of every drug label.

CONCLUSIONS:

Based on my review of the foregoing, I have reached the following conclusions to a reasonable degree of scientific and medical certainty:

1. The new drug development process and the FDA's review process for new drug applications are extensive and thorough.

2. After a drug has been approved, the FDA and the drug manufacturer continue to evaluate the risk/benefit profile of the medication and its labeling. The FDA has access to more sources of information and data, including post-marketing safety data, about drugs and classes of drugs than the individual sponsors of those medications.

3. Before seeking FDA approval to market each of the olmesartan medicines, DSI adequately and reasonably studied and tested olmesartan and the olmesartan combination medications.

4. The development of the olmesartan medicines, and their labeling, has always been science-based, accurate, and FDA-approved.

5. After approval of each olmesartan product, DSI continued to assess the safety profiles of each medication and, where appropriate, initiated labeling revisions based on new information. DSI openly evaluated new information and acted properly in securing FDA approval to ensure that olmesartan product labeling remained adequate and appropriate. This willingness is reflected in the numerous labelling changes initiated by DSI for each of its olmesartan products since the original 2002 market introduction.

6. DSI immediately and thoroughly investigated the 2009 increase in adverse event reports of celiac disease in patients taking olmesartan. DSI verified that it possessed no animal data or in-vitro data to suggest that olmesartan might predispose to celiac disease, confirmed that there

[34] 71 FR 3934.

was no indication of celiac disease in its clinical trial database, found no evidence in the medical literature to support an association of ARB therapy with celiac disease and verified that its products did not contain any gluten. DSI also considered data from ROADMAP which revealed no signal for significant GI events associated with Benicar. Based on the totality of the data at that time (as well as of today), it was not reasonable for DSI to have initiated a labeling change to include a reference to celiac disease as an adverse event finding. To have done so would have been misleading to physicians and harmful to patients, complicating GI work-ups and potentially leading to unnecessary discontinuations of olmesartan-based therapy.

7. The reasonableness of DSI's conduct is further supported by the actions of the FDA. In 2007, the FDA approved Azor, and in July of 2010, it approved Tribenzor, another olmesartan combination product, although it was aware that a question had been raised regarding the potential association between olmesartan and celiac disease in 2009. The FDA also approved DSI's request in February 2011 to add "diarrhea" as an adverse event observed post-marketing with the three olmesartan combination products. Finally, the FDA also approved olmesartan for pediatric use in February 2010 following a public advisory committee hearing held in February 2011 in which no new safety signals were identified and with no mention of a celiac or GI safety concern. At the time of each approval, despite its full authority to do so, the FDA did not require additional studies or mandate labeling changes to address the potential association between olmesartan and celiac disease or enteropathy, or any serious GI disorder. The FDA did not even initiate a TSI for the GI safety concerns related to olmesartan until mid-2012, despite this tracking system being in place since 2008.

8. DSI's decision not to initiate a labeling change for its olmesartan products was further supported by the results of the first FDA "Mini-Sentinel" query released in January of 2012 which revealed very low rates of celiac disease for all ARB agents with no difference between olmesartan and the other ARBS. The FDA expressly noted that olmesartan did not appear any different from the other ARBs and that was "reassuring."

9. It was reasonable for DSI not to conduct a new study to assess the questions related to celiac disease with olmesartan-based therapy. DSI already had an extensive randomized controlled clinical trial database, including the ROADMAP study, which was evaluated and found not to support any signal for celiac disease, enteropathy, or severe GI side effects. Due to this and the lack of any signal from other sources (lack of a mechanisms of action, lack of any enteropathy in animals, lack of a signal from other ARBs, lack of a signal from the original Mini-Sentinel), it was reasonable for DSI not to plan/conduct a new study to assess whether olmesartan was associated with celiac disease (or an enteropathy).

10. Upon learning of the Mayo case series in June 2012, DSI responded appropriately by immediately obtaining additional information on the subject patients and beginning efforts to assess whether there was any additional data which supported an association between olmesartan and the newly described "sprue-like enteropathy."

11. When DSI received a request from the FDA in July of 2012 to provide a review of all serious spontaneous reports of certain GI events associated with olmesartan within 60 days, it responded appropriately by conducting a thorough analysis of its global safety database and all the data it could gather on the patients included in the Mayo case series. Based on its analysis of the data, DSI responded to the FDA's request on September 28, 2012 and concluded that it

could not substantiate the association of olmesartan with the sprue-like illness described in the Mayo case series. Given the sound data to the contrary (lacking an association), this was a reasonable conclusion to make.

12. As of September 28, 2012, FDA was in the process of assessing the data provided by all of the ARB sponsors and FDA had opened a TSI for olmesartan in June of 2012 which would be specifically addressed at a later time. Given these circumstances, it would have been premature for DSI to have initiated a labeling change for its olmesartan products even if it had concluded that such a change might be warranted. Rather, the reasonable and prudent course of action was to await the outcome of the FDA's ongoing analysis and its specific recommendations.

13. When DSI was informed by the FDA in May of 2013 that it would require a labeling change for olmesartan products, this was based on a comprehensive analysis by the FDA of data from numerous sources (including a second Mini-Sentinel analysis) which DSI did not have access to. DSI fully cooperated with the FDA to implement the labeling change for its olmesartan products in a timely manner, with CBE submissions completed by May 31, 2013 and new labelling approved by the FDA on July 3, 2013.

14. At all times, DSI timely shared with the FDA all relevant and appropriate information concerning the potential risks of olmesartan.

15. I do not agree with Dr. Kessler's opinion that "reasonable evidence of a causal association" existed to support a change in the labeling of olmesartan products based on the 12 adverse event reports he references from 2004 through 2007, or for the totality of 60 adverse event reports he references from 2004 through 2012. The determination of whether reasonable evidence of a causal association exists to support a labelling change is a complex medical judgment. While positive dechallenge and rechallenge experience can be a factor in making this determination, multiple guidances from the FDA confirm that many factors must be taken into account. My first-hand experience as a medical officer and deputy director at the FDA, where these decisions are part of the day-to-day work of the primary review Division, support this as well. Various examples cited by Dr. Kessler in which the FDA purportedly changed drug labeling based on de/rechallenge evidence also demonstrate that the FDA takes into account many other factors before requiring a labeling change.

16. I do not agree with Dr. Kessler's opinion that DSI should have ascertained as early as 2007 that a condition later labeled as "sprue-like enteropathy" might be associated with olmesartan based on post-marketing adverse event reports. A drug company is obligated to describe adverse events as characterized by the reporter and is not to "second-guess" the information that it receives. Because GI side effects were already labeled as a possible side effect of olmesartan, infrequent reports of non-specific GI events, even if present upon de/re-challenge, would be unlikely to have been identified as any type of significant new safety signal. The difficulty in making any type of association between olmesartan and what later became known as "sprue-like enteropathy" is aptly demonstrated by the fact that the same group of doctors at the Mayo Clinic who identified this as a drug-associated disease process in 2012 failed to mention this as a drug-associated effect in 2010, despite noting that one-third of the patients in their study at that time were taking olmesartan.

17. In sum, it is my opinion that DSI, at all times, acted appropriately in assessing the potential causal association of its olmesartan products to reports of celiac disease and other GI disorders and implemented appropriate revisions to the labeling of those products in a timely manner.

Date: January 31, 2017

Marianne C. Mann, M.D.

APPENDIX A – CURRICULUM VITAE

Personal Information

Marianne Culkin Mann

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Date of Birth: March 15, 1962
Place of Birth: Towanda, PA
Citizenship: USA
Married; 3 children

Education

Graduate Medical Education

1989-1992	University of Connecticut Health Center Farmington, CT 06032 Pulmonary and Critical Care Fellowship
1988-1989	University of Connecticut Health Center Farmington, CT 06032 Internal Medicine Residency
1986-1988	Albert Einstein Medical Center Philadelphia, PA 19141 Internal Medicine Residency

Medical Education

1982-1986	Medical College of Pennsylvania Philadelphia, PA 19129 M.D. degree awarded June, 1986

Undergraduate Education

1980-1982 Lehigh University
Bethlehem, PA 18015
B.A. degree awarded June, 1984
(6-year accelerated BA/MD program)
Graduated cum laude

Societies, Licensure and Board Certification

Pennsylvania State Medical License MD 038630-E
DEA # BM1030105
Board Certified in Internal Medicine 1989-present
Board Certified in Pulmonary Medicine 1992-2002/Recertified Through 2014
Board Certified in Critical Care Medicine 1993-2003

Honors

FDA Awards/Honors (selective list, not all)
2002 CDER's Excellence in Communication Award *for comprehensive and collaborative team effort in working to address a safety concern regarding bacterial contamination in multi-dose albuterol vials.*
1999 FDA Commendable Service Award *for exceptional performance including interagency collaboration in the priority review of the rifapentine application, the first new drug approved for pulmonary tuberculosis in 25 years.*
1999 FDA Commendable Service Award *for outstanding commitment and cooperation between FDA staff in handling post-marketing events noted with the drug Viagra*
1998 FDA Award of Merit *for enhancing the design of wasting trials through a cooperative partnership involving government regulators, industry representatives, clinical academicians and patients who have wasting.*
1998 DHHS Secretary's Award for Distinguished Service *for enhancing the design of wasting trials through a cooperative partnership involving government regulators, industry representatives, clinical academicians and patients who have wasting.*
1996-1997: Selected for the Center for Drug Evaluation Leadership Fellows Program

Post Graduate Residence/Fellowship Training
1987: Upjohn Achievement Award for Outstanding First Year Medical Resident

Medical School (MCP)
Received Honors in Otolaryngology, Ambulatory Medicine and Urology

Undergraduate (Lehigh University)
Dean's List
William's Essay Award

Hospital Appointments/Employment
June of 2004-present

Clinical Drug Development & Regulatory Consultant
I work independently as a drug development and regulatory consultant. The majority of my work is in the area of pulmonary drug development for conditions such as asthma, COPD, and cystic fibrosis, as well as the field of allergy. My work extends from pre-IND meetings throughout approval and post-approval commitments. I am very familiar with pulmonary drug development or inhaled therapies and the challenges they pose. I have served on many drug advisory and drug safety boards. I have served on many mock advisory panels for products in the pulmonary space, but also for other indications. Since 2014, I've worked specifically with Pharmapprove as a consultant, helping prepare sponsors for FDA advisory panels. In May of 2013, I presented at an FDA panel meeting, presenting findings of adjudicated anaphylaxis events for a testosterone product made by Endo Pharmaceuticals. I have a very sound understanding of how the FDA balances risk/benefit profiles of drugs based on my work At the Agency, as well as from my consulting experience over the past decade. I have a strong foundation in advisory panel preparation and execution, but am familiar with helping sponsors meet their pre-IND, EOP-2, and pre-NDA goals as well.

1996-2004
Volunteer Staff Pulmonologist
National Naval Medical Center
Bethesda, MD
I evaluated patients in an out-patient pulmonary clinic for conditions like asthma, chronic obstructive pulmonary disease, sarcoidosis, and abnormal chest x-rays. I was responsible for teaching pulmonary fellows and attended an outpatient clinic 4 hours each week. I also taught a course to medical students on physical examination while volunteering.

2003-2004
Branch Chief
Respiratory Disease Branch (RDB)
Division of Microbiology and Infectious Diseases (DMID)
National Institute of Allergy and Infectious Diseases (NIAID)
National Institutes of Health
Bethesda, MD
With a team of 12 professionals, I helped this branch of NIAID sponsor research in the areas of respiratory infectious diseases including influenza, SARS, tuberculosis, RSV, and a variety of bacterial and other respiratory pathogens. We used existing contract and grant funding mechanisms and, if necessary, created new RFPs (requests for proposals) or RFCs (requests for contracts) in order to help make strides in the area of respiratory infectious disease. My role was to facilitate and lead this process, and particularly to ensure that the clinical trials being undertaken (under INDs and NDAs) were well designed and safely run.

2000-2003
Deputy Director
Division of Pulmonary and Allergy Drug Products

Center for Drug Evaluation and Research
Food and Drug Administration
Rockville, MD
My scientific responsibilities in this position included helping to lead the division in its work, as well as perform some primary review. In this position, there is extensive experience reviewing or supervising reviews of clinical protocols from the early phases of drug development through post-marketing for drugs to treat asthma, allergic rhinitis, chronic obstructive pulmonary disease, cystic fibrosis, and other respiratory/allergic conditions. Clinical trial designs were carefully evaluated for their ability to demonstrate effectiveness and maintain patient safety. Data from these trials are then interpreted to support the potential approval of products and develop appropriate drug labeling. The spectrum of drug products included traditional inhaled therapies (bronchodilators, inhaled corticosteroids, etc), phosphodiesterase-4 inhibitors, leukotriene inhibitors, and novel molecular entities involving new mechanisms of action. This job entailed managerial and leadership skills, as well as a broad understanding of drug development from phase 1 through phase 4.

My professional responsibilities as Deputy Director included representing the Agency at meetings with industry, Congress, the media, and the public Several times each week, I chaired various meetings with industry and I was regularly involved in discussions to negotiate scientific and/or regulatory issues related to clinical drug development. I presented at several FDA Open Public Advisory Committee meetings and was asked to instruct new FDA staff how to prepare for such presentations in a newly introduced CDER Staff College Course on preparing for FDA advisories. I presented at several professional meetings on behalf of the Agency (e.g. discussing FDA's pediatric initiatives at the 2002 American Thoracic Society's annual meeting). I served as the Division's primary point of contact for consults from within the Agency (including consults with the Division of Drug Marketing, Advertising, and Communications or DDMAC) as well as helping respond to congressional inquiries, citizen's petitions, requests for IND waivers, and inquiries from the public. My role involved frequent collaboration with professionals across the Agency, (Center for Devices and Radiologic Health, the Center for Food Safety and Nutrition, and the Center for Biologic Evaluation and Research) on a number of initiatives related to the Agency's mission.

My managerial responsibilities in this position included the being the direct supervisor of several employees, and helping the Director with the supervision and management of a staff of approximately 50 people, organizing a guest lecture series for the Division's Scientific Rounds, coordinating yearly retreats, and hiring new staff.

1998-2000
Deputy Director
Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
Rockville, MD

During my two years as Deputy Director in the Division of Reproductive and Urologic Health, I had to learn about a new area of clinical medicine that was unrelated to my expertise as a pulmonologist and intensivist, but still related to drug development. A unique and highly visible challenge I encountered in this role was taking on a primary role in dealing with the post-marketing reports of death related to the use of the approved drug Viagra. This required interactions at the level of the FDA Commissioner, handling press releases and speaking with the media to define the Agency's approach to ensure safe use of this high profile medication. Another challenge was meeting frequently with Congressional staff members to discuss and defend a controversial position the Agency took on the use of inhaled terbutaline by pregnant women in the out-patient setting. As Deputy Director, I often served a primary role in addressing consultative requests from within the Agency, including the Center for Devices and Radiologic Health (CDRH), and the Division of Drug Marketing, Advertising and Communications (DDMAC).

1994-1997
Medical Officer
Division of Antiviral Drug Products/Division of Special Pathogens and Immunologic Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
Rockville, MD

In this position, I developed the primary skills necessary for an FDA clinical reviewer. This included achieving a basic understanding of clinical trial designs, statistics, drug law, pharmacokinetics and pharmcodynamics, and preclinical toxicology. I provided detailed clinical reviews of protocols involving AIDS, tuberculosis and non-tuberculous mycobacteria, respiratory syncitial virus, chlamydia TWAR, cystic fibrosis, pneumocystic carinii, and a wide variety of bacterial respiratory pathogens. Specifically, my clinical review directly supported the approval of rifapentine (the first drug approved in 25 years to treat tuberculosis), and the approval of the MTD test (a rapid diagnostic test for the detection of tuberculosis in the sputum). The MTD test was the first PCR test for tuberculosis that was FDA-approved, and I presented the clinical data for this test at the FDA CDRH Advisory Panel Meeting. My experience as a primary clinical reviewer helped me develop a strong knowledge base regarding the microbiological and clinical issues related to the field of respiratory pathogen research, with an emphasis on tuberculosis.

One accomplishment I am particularly proud of is my coordination of a workshop to address the selection of meaningful clinical endpoints in trials for wasting (due to cancer, AIDS, etc). This involved input and support from NIAID's extramural program, the FDA, the CDC, from drug sponsors, academicians and patients who suffer from wasting. Another achievement was my work with Dr. Henry Masur, Dr. Fred Ognibene, and others at the NIH that resulted in the publication of a paper regarding the lack of specificity and clinical relevance of the finding of positive CMV cultures in bronchoalveolar lavage fluid from patients who are HIV infected.

1993-1994

Staff Pulmonologist and Internist
Kimbrough Army Community Hospital
Fort Meade, MD
My responsibilities in this job included serving as a primary care physician for out-patients in the general medical clinic, and serving as ICU director for an active 6-bed intensive care unit.

1992-1993
Staff Pulmonologist
Hospital for Special Care
New Britain, CT
My responsibilities in this job included serving as a staff pulmonologist and caring for 40 patients in a chronic respiratory care unit. Teaching residents in the ICU was also a primary responsibility in this job.

Publications

Meyer R, Mann M. Pulmonary Oil Micro-embolism (POME) Syndrome: A review and summary of a large case series. Accepted January 2015 for publication, Current Medical Research and Opinion (publication date pending).

Gross N, Mann M. The COPD Pipeline XVI: Clinical Trials and Changes in the Drug Approval Process. Journal of Chronic Obstructive Pulmonary Disease 2012; 9: 310-312.

Mann M, Chowdhury B, Sullivan E, Nicklas R, Anthracite R, Meyer R. Serious Asthma Exacerbations in Asthmatics Treated with High Dose Formoterol. Chest 2003;124:70-74.

Koller E, Mann M, Malozowski S, Bacsanyi J, Gildbert C. Aseptic Necrosis in HIV seropositive patients: a possible etiologic role for megestrol acetate. AIDS Patient Care STDS 2000;14(8):405-410.

Mann M. Clinical Trials for the Treatment of Secondary Wasting and Cachexia. J. Nutrition 1999; 129:303S-305S.

Mann M, Piazza-Hepp T, Koller E, Struble K, Murray J. Unusual Distributions of Body Fat in AIDS Patients: A Review of Adverse Events Reported to the Food and Drug Administration. AIDS Patient Care STDS 1999; 13(5):287-295.

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Mann M, Shelhamer JH, Masur H, Gill VJ, Travis W, Solomon D, Manischewitz J, Stock F, Lane HC, Ognibene FP. Lack of Clinical Utility of Bronchoalveolar Lavage Cultures for Cytomegalovirus in Patients with HIV Infection. Am J Respir Crit Care Med 1997;155(5):1723-1728.

Mann M, Murgo A, Malozowski S, Koller E, Bacsanyi J. Glucocorticoid-like Activity of Megestrol Acetate. Arch Int Med 1997;157:1651-1656.

Scalise P, Mann M, Votto J, McNamee MJ. Severe Hypothermia in the Elderly. Conn Medicine 1995;59(9):515-517.

Mann M, Patel K, Reardon J, Goldstein M, Godar TJ, ZuWallack RL. The Influence of Spring and Summer New England Meteorologic Conditions on the Respiratory Status of Patients with Chronic Lung Disease. Chest 1993;103:1369-74.

Mann M, Asuncion C. Simultaneous Primary Lung Sarcoma and Carcinoma. J Surg Onc 1992;49:270-72.

Mann M, Eliasson O, Patel K, ZuWallack RL. An Evaluation of Severity-Modulated Compliance with q.i.d. Dosing of Inhaled Beclomethasone. Chest 1992;102:1342-46.

Mann M, Eliasson O, Patel K, ZuWallack RL. A Comparison of the Effects of b.i.d. and q.i.d. Dosing on Compliance with Inhaled Flunisolide. Chest 1992;101:496-99.

Mann M, Votto J, Kambe J, McNamee MJ. Management of the Severely Anemic Patient who Refuses Transfusion: Lessons Learned During the Care of a Jehovah's Witness. Ann Intern Med 1992;117:1042-48.

Books/Chapters

Mann M, Votto J, Kambe J, McNamee MJ: Management of the Severely Anemic Patient who Refuses Transfusion. In Clinical Medical Ethics Cases and Readings. University Press of America. 1995: 273-284.

Abstracts/Presentations

Mann M, Patel K, Elliason O, ZuWallack RL: A Comparison of the Effects of b.i.d. and q.i.d. Dosing on Compliance with Inhaled Flunisolide. Abstract and formal presentation at the1992 ACCP Meeting, San Francisco.

Mann M, Elliason O, Patel K, ZuWallack RL: An Evaluation of Severity Modulated Compliance with Inhaled Beclomethasone. Abstract at the1992 ATS Meeting, Miami.

Votto J, Brancifort J, Mann M, Wollschlager C: A 13 Year Experience in a Long Term Ventilator Unit. Abstract at the 1993 ACCP Meeting, Orlando.

Wollschlager C, Brancifort J, Mann M, Votto J: Evaluation of Premature Discharges from an Inpatient Pulmonary Rehabilitation Program. Abstract at the 1993 ACCP Meeting, Orlando.

Mann M, Koller E, Malozowski S, Murgo A, Bacsanyi J: The glucocorticoid-like activity of megestrol acetate: report on 56 cases. Abstract at the 10th International Congress on Endocrinology meeting in June, 1996, San Francisco.

Koller E, Green MS, Mann M: Thrombotic Events in AIDS Patients on Megestrol Acetate. Abstract and formal presentation at the Second International Conference on Nutrition and HIV Infection in April 1997, Canne-France.

Mann M, Piazza-Hepp T, Koller E, Gilbert C: Abnormal Fat Distribution in AIDS Patients Following Protease Inhibitor Therapy: FDA Summary. Abstract at the 5th Conference on Retroviruses and Opportunistic Infections in February 1998, Chicago.

Ahmad S, Graham D, Toyer D, Wassel R, Mann M: Comparison of Pulmonary Toxicity Risks with Antiandrogens. Journal of Pharmacoepidemiology and Drug Safety; Volume 9, Supplement 1, page S121, 2000.

Formal Lectures and Presentations

1/26/96: FDA Office of Device Evaluation, Division of Clinical Laboratory Devices: Advisory Committee presentation on the Roche Amplicor Rapid Diagnostic Detection Device for Tuberculosis in Rockville, MD.

1/21/97: "CDER's approach to new antituberculous drugs" Presented to Chinese Delegation of TB Control at Parklawn Building in Rockville, MD.

5/23/97: "Approved pharmacologic therapies for wasting" presented at the Workshop on Clinical Trials for the Treatment of Secondary Wasting and Cachexia at Natcher Auditorium, NIH Campus, Bethesda, MD.

11/21/97: FDA Advisory Committee presentation on inhaled tobramycin (TOBI®) for the Treatment of Cystic Fibrosis.

1999-present: FDA panel member/instructor for the course "Drug Development: A Condensed Overview" for multiple PERI courses (approximately 2 to 3 each year).

1/24/01: Moderator of CDER Scientific Rounds discussing the Use of a Placebo-Controlled Trial in Latin America for Development of a New Surfactant.

10/4/01: Presenter at the FDA's "Workshop on Non-Inferiority Trials" where the Division's experience with designing surfactant trials was presented.

6/5/01, 11/6/01, 10/3/02, 2/25/03: Teacher at FDA Course "Presenting at Advisory Committee Meetings" lecture entitled "Crafting your Presentation"

Chair and Organizer or Facilitator
5/22-5/23/97: Workshop on Clinical Trials for the Treatment of Secondary Wasting and Cachexia at Natcher Auditorium, NIH Campus, Bethesda, MD.

7/97-7/00: Chairman of the FDA Wasting Working Group which includes approximately 15 members who meet monthly to discuss various regulatory and scientific issues in relation to wasting trials.

4/98—4/99: Member of FDA Viagra Working Group which includes approximately 8 members who meet weekly to every two weeks to discuss various regulatory and scientific issues related to Viagra.

6/02: Facilitator for FDA Risk Management Workshop entitled "The Label and Beyond" held on June 30, 2002 at the University of Maryland, Shady Grove.

2004-2013: Co-Director of the 2.5 day PERI Course entitled "Clinical Development of Drugs for Asthma and COPD" held each year in Baltimore, Maryland or in Vienna, Virginia. In 2011, I participated in the course, giving two lectures, but I was not a co-director. In 2012, I resumed directing the course (by myself). In 2013, we are planning an October meeting in Vienna Virginia. Each year, DPARDP sends a member of the Division to also present and answer questions. This course enhances my ability to stay directly in touch with the FDA's Division of Pulmonary and Allergy (and Rheumatology) Drug Products, and keep afresh of acceptable endpoints and trial designs for COPD and asthma.

FDA Courses (a sample list, not comprehensive)
Basic Statistical Methods, CDER Staff College, Fall 1994
Elementary Pharmacokinetics, CDER Staff College, Fall 1994
Regulatory Science, CDER Staff College, Spring 1995
Introduction to Clinical Trials, CDER Staff College, Spring 1995
NDA Game: FDA Industry Interaction in Drug Development, February 16-17, 1995
Quality of Life, CDER Staff College, Spring 1996
Advanced Statistics/Excel Applications, CDER Staff College, August 19-22, 1997
FAME I Leadership Course, January 26-30, 1998
The Successful Negotiator, Fall 2000
FAME II Leadership Course, June of 2000
FDA Personnel Practices for Supervisors, July of 2001
Communication Skills, May 2002
Successful Searching on the Net, July 2002

FDA Working Groups and Committees (a sample list, not comprehensive)
2001-2003: Oncology Coordinating Committee Member
2001-2002: Shelf Chemicals Working Group Member
2002-2003: PDUFA 3 Implementation Working Group Member
2002-2003: NICHD-FDA Newborn Initiative Group Member

APPENDIX B – MATERIALS REVIEWED

Expert Reports

Expert Report, Appendices, and Schedules of David Kessler, M.D.

Deposition Transcripts

Deposition Transcript and Exhibits of Diane Benezra-Kurshan (03/18/2016)
Deposition Transcript and Exhibits of Herve Caspard (04/07/2016)
Deposition Transcript and Exhibits of Manini Patel (05/04/2016)
Deposition Transcript and Exhibits of Alan Feldman (05/06/2016)
Deposition Transcript and Exhibits of Crawford Parker (05/25/2016)

Medical Literature

Medical literature includes but is not limited to the medical literature cited throughout my Report.

Bates Documents

OLM-DSC-0000091180
OLM-DSC-0000096357
OLM-DSC-0000096368
OLM-DSC-0000096385
OLM-DSC-0000096402
OLM-DSC-0000096605
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Other Sources

FDA regulations, guidances, and other materials, including materials related to olmesartan, at fda.gov and other publicly available sites.

All other documents cited in my Report